NATIONAL BREAST
AND OVARIAN
CANCER CENTRE

NEOADJUVANT CHEMOTHERAPY IN OVARIAN CANCER:

A SYSTEMATIC REVIEW

APRIL 2008

PREPARED BY NATIONAL BREAST AND OVARIAN CANCER CENTRE

FUNDED BY THE AUSTRALIAN GOVERNMENT
DEPARTMENT OF HEALTH AND AGEING

Neoadjuvant chemotherapy in ovarian cancer: a systematic review
was prepared and produced by:

National Breast and Ovarian Cancer Centre

Level 1, Suite 103, 355 Crown Street, SURRY HILLS NSW 2010, Australia

Telephone: +61 2 9357 9400

Fax: +61 2 9357 9477

Website: www.nbocc.org.au

Email: directorate@nbocc.org.au

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ISBN Online: 978-1-74127-124-9

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Recommended citation

National Breast and Ovarian Cancer Centre. Neoadjuvant chemotherapy in ovarian cancer: a systematic review. National Breast and Ovarian Cancer Centre, Surry Hills, NSW, 2008.

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National Breast and Ovarian Cancer Centre website: www.nbocc.org.au**

National Breast and Ovarian Cancer Centre is funded by the
Australian Government Department of Health and Ageing.

ACKNOWLEDGEMENTS

National Breast and Ovarian Cancer Centre gratefully acknowledges the support of all the individuals and groups who contributed to the development of this review.

Funding

Funding for the development of this review was provided by the Australian Government Department of Health and Ageing.

Review Group

This review was developed with input from a multidisciplinary review group:

Ms Kathryn Nattress

Associate Professor Andreas Obermair

Dr Sudarshan Selva-Nayagam

National Breast and Ovarian Cancer Centre Staff

The following people were involved in the development of this review:

Ms Rosemary Vagg

Ms Katrina Anderson

Ms Jane Francis

Dr Karen Luxford

Dr Elmer Villanueva

Ms Katie Rampling

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LIST OF ABBREVIATIONS

ASCO	American Society of Clinical Oncology
CI	Confidence Interval
DFS	Disease-Free Survival
EOC	Epithelial Ovarian Cancer
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
GOG	Gynecologic Oncology Group
HR	Hazard Radio
ICU	Intensive Care Unit
NAC	Neoadjuvant Chemotherapy
NBCC	National Breast Cancer Centre
NBOCC	National Breast and Ovarian Cancer Centre
NHMRC	National Health and Medical Research Council
OS	Overall Survival
PFS	Progression-Free Survival
PS	Primary Surgery
QoL	Quality of Life
RCT	Randomised Controlled Trial
SGO	Society of Gynecologic Oncologists

EXECUTIVE SUMMARY

A number of potential advantages have been proposed to support the use of neoadjuvant chemotherapy for the treatment of women with ovarian cancer. A systematic review has been undertaken to identify evidence for the administration of neoadjuvant chemotherapy before cytoreductive surgery is performed. Twenty-eight articles were eligible for inclusion in the review (two systematic reviews and 24 comparative trials).

Based on the systematic review, there is no conclusive evidence from randomised controlled trials to suggest that neoadjuvant chemotherapy for ovarian cancer followed by surgery is more effective than conventional surgery followed by chemotherapy.* All but one of the reported trials are classified as level III evidence, and there are difficulties in comparing the results from trials due to variations in protocols and reported outcomes.

Further clinical trial information is needed to clarify the benefits and harms of neoadjuvant chemotherapy for the treatment of women with ovarian cancer.

*Note: Since the completion of this review, a review undertaken by the Cochrane Collaboration (2007) also supported this conclusion.[1]

INTRODUCTION

National Breast and Ovarian Cancer Centre (NBOCC) produces a range of evidence-based publications including clinical practice guidelines, evidence reviews, research reports and consumer resources in a context of continuing changing evidence.

NBOCC has produced a number of evidence reviews on new and emerging treatments and/or technologies. After consultation with NBOCC national and international advisors, the use of neoadjuvant chemotherapy in the management of ovarian cancer was identified as a priority evidence review topic.

Neoadjuvant chemotherapy is defined as chemotherapy administered as initial treatment and followed by surgery. Further chemotherapy may be administered after surgery is performed (adjuvant chemotherapy). Neoadjuvant chemotherapy has been used in oncology to reduce the extent of disease or to improve patient performance status.

The NBCC's* *Clinical practice guidelines for the management of women with epithelial ovarian cancer*, 2004, state that primary cytoreduction is considered the initial treatment of choice for women with ovarian cancer and that neoadjuvant chemotherapy and interval cytoreduction may be considered if optimal primary cytoreduction was not achieved.[2]

A number of potential advantages have been proposed to support the use of neoadjuvant chemotherapy including:

- increased rate of optimal cytoreduction
- less extensive surgery
- reduced blood loss
- reduced morbidity
- reduced hospital stay
- improved quality of life.

The aim of this review is to identify the evidence for the administration of neoadjuvant chemotherapy *before* cytoreductive surgery is performed for epithelial ovarian cancer. The benefits and harms of neoadjuvant chemotherapy, compared with primary surgery, will be discussed. This review is not intended as a clinical practice guideline or treatment recommendation.

In February 2008, National Breast Cancer Centre (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC).

METHODS

The research question addressed by this systematic review was:

> *How does neoadjuvant chemotherapy compare to primary surgery for treatment of ovarian cancer and extra-ovarian disease?*

INCLUSION CRITERIA

Population
Women with ovarian cancer or extra-ovarian disease (peritoneal cancer or fallopian tube cancer).

Intervention
- Neoadjuvant chemotherapy (NAC)

Defined as chemotherapy administered as initial treatment and followed by surgery. Further chemotherapy may be administered after surgery is performed.

Comparison
- Primary surgery (PS)

Also referred to as primary cytoreductive surgery and defined as surgery performed as initial treatment, often followed by adjuvant chemotherapy.

Outcomes
- overall survival (OS)
- progression-free survival (PFS)
- morbidity
- adverse events
- quality of life (QoL).

LITERATURE SEARCH

A systematic literature search was conducted in January 2007 to identify comparative trials which addressed the inclusion criteria. The search was updated in June 2007. The search was conducted over several databases/sources (see Appendix 1), including:
- Medline (Ovid)
- EMBASE
- Pubmed
- EBM reviews (Ovid)
- CINAHL (Ovid)
- Cochrane Library, Issue 2, April 2007.

In addition to the above databases, several conference, guidelines and health technology assessment websites were searched for relevant information.
Conference sites searched included:
- American Society of Clinical Oncology (ASCO)
- Society of Gynecologic Oncologists (SGO).

A list of the guidelines, clinical trials and health technology assessment websites searched can be found at Appendix 2. Additional papers identified from personal files and the reference lists of included papers were also sourced.

The search strategy used combined key terms that described ovarian cancer and neoadjuvant chemotherapy (see Appendix 3). The search was limited to trials conducted in humans that were published from January 1990 to June 2007, in the English language.

After the removal of duplicate citations and the addition of further citations sourced, a total of 332 unique citations remained. The titles and abstracts of these citations were assessed by two independent reviewers to determine eligibility for the current review based on the criteria described above. Ineligible studies were classified using the exclusion criteria below. For citations that provided insufficient information to assess eligibility, the full text was retrieved for assessment.

Exclusion Criteria

Papers were excluded if they met any of the following criteria:

- not an original clinical study — publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters
- inappropriate population — studies conducted in a population other than patients with ovarian cancer or extra-ovarian disease
- inappropriate intervention — studies not investigating neoadjuvant chemotherapy as defined in inclusion criteria, i.e. trials investigating use of chemotherapy followed by interval cytoreduction (or interval debulking) in patients who had previously undergone suboptimal cytoreductive surgery were not included in this review.
- inappropriate design — non-comparative studies, i.e. case series were excluded
- not English language
- published prior to 1990.

Based on these criteria, 184 articles were excluded. The full text of the remaining 148 citations were retrieved and assessed to identify which met the inclusion criteria for the review. After full text assessment, 28 citations were identified as eligible for the current review (see Appendix 4). Of the included citations, there were two systematic reviews and 24 comparative trials that addressed the research question (two trials were reported by more than one citation).

No guidelines or health technology assessment reports were identified on this topic.

DATA EXTRACTION

Data extraction was performed independently by two reviewers and compared to ensure accuracy and consistency. Any discrepancies were discussed by the reviewers to arrive at a consensus decision. Where multiple citations existed for one trial, data was extracted from the latest available publication. Descriptive data extracted from the studies included patient characteristics, assignment to and details of treatment arms, and enrolment details. Outcome data extracted from the studies included optimal cytoreduction, disease-free and overall survival. Morbidity data extracted from the studies included blood loss, duration of surgery, hospital stay and post-operative complications.

QUALITY ASSESSMENT

The majority (96%) of the included studies are non-randomised comparative studies, namely case-control and cohort studies, which represent level III evidence, as defined by the National Health and Medical Research Council (NHMRC), Levels of Evidence,[3] see Appendix 5. Only one randomised controlled trial (RCT) (level II) has reported, in abstracts only, with insufficient information provided to determine the quality of this study.

The majority (70%) of the trials were conducted retrospectively. Patient populations were often not well balanced between treatment arms. Many of the trials were affected by selection bias, with patients selected for the neoadjuvant group likely to have a poorer prognosis, results from these studies must be interpreted with caution.

RESULTS

INCLUDED SYSTEMATIC REVIEWS

Bristow and colleagues

Bristow *et al* published both a systematic review[4] and meta-analysis[5] on neoadjuvant chemotherapy and interval cytoreduction for advanced ovarian cancer.

Systematic review, 2007[4]

This systematic review included trials published between 1989 to mid-2006. Twenty-six studies (both comparative studies and case series) reporting on neoadjuvant chemotherapy administered in lieu of primary cytoreductive surgery were identified. The studies included were all considered level III evidence, with 12 retrospective analyses, eight retrospective case-control studies, four phase I studies and two phase II studies.

The authors separated the neoadjuvant trials into three categories based on the following outcomes:

I) Survival after neoadjuvant chemotherapy is inferior to survival after primary cytoreductive surgery.
II) No significant difference in survival outcome between neoadjuvant chemotherapy and a less than maximal primary cytoreductive surgical effort.
III) Neoadjuvant chemotherapy inclusion criteria with limited validation in predicting surgical outcome.

Ten studies found survival in patients who received neoadjuvant chemotherapy to be inferior to survival in patients who had primary cytoreductive surgery. For studies that did not report a comparison group, results were compared to results of the Gynecologic Oncology Group (GOG) trial protocol #111,[6] with median survival of 24 months for cisplatin/cyclophosphamide chemotherapy or 36 months for cisplatin/paclitaxel chemotherapy.

Nine studies reported no significant difference in survival between neoadjuvant chemotherapy and a less than maximal primary cytoreductive surgical effort (where maximal primary cytoreduction is defined as <2cm residual disease).

Seven studies were classified as studies that had inclusion criteria for neoadjuvant chemotherapy with limited external validity for predicting a suboptimal primary surgical effort. The authors questioned whether the beneficial survival outcome of patients receiving neoadjuvant chemotherapy observed in these trials could have been achieved in these patients had they been submitted to a maximal attempt at primary cytoreductive surgery.

The authors concluded that neoadjuvant chemotherapy represented a viable alternative management strategy for patients with unresectable disease (determined by an experienced ovarian cancer surgical team). At this time, the data suggested that patients treated with neoadjuvant chemotherapy had an inferior survival outcome compared to patients treated with successful up-front cytoreductive surgery.

Meta-analysis, 2006[5]

The meta-analysis conducted by Bristow and Chi focussed on platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer.

Twenty-two cohorts of patients (from 21 studies) were included in the meta-analysis. Fewer trials are included in the meta-analysis than the systematic review because the literature search for the meta-analysis was completed before the systematic review, only including papers up to 2005.

The mean weighted median survival time was 24.5 months (range 10–42 months). Results of the cohorts were analysed to determine the relationship between median survival and maximal cytoreduction, number of chemotherapy cycles, taxane use, stage IV disease, year of publication and median cohort age. Relationships were calculated using simple linear regression analysis.

Maximal cytoreduction, larger percentages of taxane use, and later publication date were associated with increases in median survival. Each 10% increase in proportion of patients with maximal cytoreduction (defined in the trials as residual disease either ≤1cm or ≤2cm) was associated with a 1.9 month increase in survival ($p=0.027$). Each 10% increase in proportion of taxane use was associated with a 1.6 month increase in median survival time ($p<0.0005$). Every one-year increment in publication date was associated with an estimated 1.1 month increase in median survival time ($p=0.004$).

Increasing cycles of chemotherapy and larger percentage of stage IV disease were associated with decreases in median survival. Every incremental chemotherapy cycle was associated with a 4.1 month decrease in median survival ($p=0.046$). Each 10% increase in proportion of stage IV patients was associated with an estimated 2.3 month decrease in median survival time ($p=0.002$).

There was no significant association found between median cohort age and median survival ($p=0.448$).

The authors concluded that neoadjuvant chemotherapy, in lieu of primary cytoreduction, was associated with inferior overall survival compared to initial surgery, although this does not appear to be strongly supported in the meta-analysis. The authors also state that increasing percent maximal cytoreduction is positively associated with median cohort survival. However, the negative survival effect of increasing the number of chemotherapy cycles prior to interval surgery suggests that definitive operative intervention should be undertaken as early in the treatment program as possible.

INCLUDED STUDIES

The primary research question of this review was to compare neoadjuvant chemotherapy to primary surgery in relation to the defined outcomes (overall survival, progression-free survival, morbidity, quality of life and adverse events).

Twenty-four comparative trials were identified as eligible for this review. Fifteen of these trials were included in the previous Bristow systematic review.[4] The NBOCC review includes only comparative studies identified in the previously mentioned systematic review that met the defined inclusion criteria. Eleven of the trials included in the Bristow review[4] were excluded from the current review due to either being a case series, published prior to 1990 or if the trial did not meet the same definition of neoadjuvant chemotherapy. The current review provides information on seven additional trials, which had been published after the Bristow literature search and therefore were not included in that previous review.[7-13] Four of these trials have reported in full-text peer-reviewed publications,[8,9,12,13] the remaining three[7,10,11] have been published as abstracts only. This review also includes two additional trials published in 2005 that were not included in the Bristow review[14,15] (likely excluded from the Bristow review because they do not report on the median survival time of individual patient cohorts).

Details of the additional trials are in Table 1, details of the trials included in both the Bristow review and the NBOCC review are in Appendix 6.

Survival and optimal cytoreduction data have been reported in the previous systematic review/meta-analysis, therefore most information in this section relates to the additional studies identified. Morbidity data had not been reported extensively in the Bristow review, therefore data from all trials are included in the current review.

DESCRIPTION OF STUDIES

Only one randomised controlled trial[7] (RCT) was identified that had reported results (presented at the ASCO 2006 and 2007 meetings). This RCT was not included in the previous systematic review. The remaining trials identified were comparative studies, either cohorts or case-control studies (level III-2), most of these were conducted retrospectively.

Most of the studies identified included small numbers of patients, often with many more patients in the control arm than the NAC arm, see Table 1 and Appendix 6.

All trials investigated the use of platinum-based chemotherapy. Most trials reported similar use of taxanes between the treatment and control groups.

Of the trials not included in the Bristow systematic review,[4] one compared neoadjuvant chemotherapy to patients receiving suboptimal cytoreductive surgery.[8] The remaining trials compared neoadjuvant chemotherapy to primary surgery (planned optimal cytoreduction). The three trials that have reported as abstracts only have limited information on study groups, however they appear to have a control group of patients who were able to be optimally cytoreduced.

PATIENT CHARACTERISTICS

While the search strategy undertaken for this review was to include both ovarian cancer and extra-ovarian disease, the majority of the trials identified only enrolled patients with advanced ovarian cancer, defined as FIGO stage IIIC or IV, who had no medical contraindications to surgery. One trial[11] enrolled patients with stage IIIC and IV ovarian, tubal and peritoneal cancer.

The majority of patients in the neoadjuvant arms were assigned to this treatment group after being identified as poor surgical candidates with ‘unresectable’ tumours. Whether a patient could

be optimally debulked was determined by exploratory laparoscopy, laparotomy or diagnostic imaging. Other reasons for assignment to neoadjuvant chemotherapy included if the patient was medically unfit for primary or aggressive surgery, or had a poor performance status. Due to these reasons, patients in the neoadjuvant arms tended to be older and more likely to have stage IV disease. In some trials, not all patients assigned to the neoadjuvant chemotherapy arms went on to receive cytoreductive surgery, either due to progression of disease or patients still being considered unresectable after NAC.

Table 1. Characteristics of papers not included in Bristow review[4]

Trial	Treatment	FIGO stage	n	Follow-up	Platinum based chemo-therapy	Taxane use	Chemo-therapy cycles prior to surgery
Kumar 2007[7] abstract	NAC		44*	41 mths	100%		3
	PS		56*		100%		
Rosa 2007[8] paper	NAC	III: 69% IV: 31%	42	20 mths	100%	50%	5
	PS	III: 73% IV: 27%	348		100%	58%	
Hou 2007[9] paper	NAC	IIIC: 46% IV: 54%	63		100%	58%	6
	PS	IIIC: 19.2% IV: 20.2%	109		100%	94%	
Milam 2007[10] abstract	NAC	IV: 41%	29		100%		3
	PS	IV: 21%	197		100%		
Silins 2007[11] abstract	NAC		51		100%	67.1%	-
	PS		138		100%	79.7%	
Giannopoulos 2006[12] paper	NAC	IIIC: 71.4% IV: 28.6%	35		100%		3
	PS	IIIC: 89.7% IV: 10.3%	29		100%		
Angioli 2006[13] paper	NAC		25	22.4 mths	100%		3
	PS		53		100%		
Bidzinski 2005[14] paper	NAC	III: 94% IV: 6%	50	35 mths	100%	100%	3 or 6
	PS	III: 93% IV: 7%	269	35 mths	100%	100%	NA
Brunisholz 2005[15] paper	NAC	IV: 100%	9	29.5 mths	100%	33%	3 or 4
	PS	IV: 100%	14	11.5 mths	100%	14%	NA

NA–not applicable; NAC–neoadjuvant chemotherapy; PS–primary surgery
*refers to number of patients who have completed treatment at this analysis

OUTCOMES

OVERALL SURVIVAL

All trials identified

In the majority of the trials, there did not appear to be a statistically significant difference in overall survival between patients who had neoadjuvant chemotherapy compared to those who had primary surgery (see Table 2). Median follow-up ranged from 12 to 41 months. Overall median survival ranged from 13 to 53 months in the NAC arms and 22 to 55 months in the control arms.

Two trials reported on five-year overall survival (OS) with similar rates seen between the NAC arm and the PS arm.[15,16] Two trials reported three-year OS, with one trial reporting a significantly lower rate in the NAC arm compared to PS[17] and the other reporting no significant difference between NAC and PS.[18] Two trials reported two-year OS rates, one with no significant difference

observed between treatment arms,[19] the other found two-year OS better in the NAC arm; however, this trial did not report the actual survival rates or median survival length.[15]

Not all patients assigned to the neoadjuvant arms went on to receive surgery. Reasons given included the patient not responding to chemotherapy, progression of disease or if the patient was still considered 'unfit' for surgery. Survival was often reported including these patients due to intention-to-treat analysis. These results often differed from when only patients who had neoadjuvant chemotherapy followed by surgery were compared to the primary surgery group. For example, Steed compared a subset survival analysis of only NAC patients who had surgery and PS patients (28 matched pairs) and found there was no overall survival difference between the groups (HR: 1.43; 95% CI: 0.53, 3.88; p=0.48).[17] (Further information on the NAC patients who did not have surgery is provided in the subgroup analyses section later in the report.)

Table 2. Overall survival outcomes

Trial	Median follow-up		Median overall survival			% survival by years of follow-up			
	PS	*NAC*	*PS*	*NAC*	*p-value*	*Years*	*PS*	*NAC*	*p-value*
Kumar 2007[7]	41 mths	41 mths	42 mths	29 mths	0.07				
Rosa 2007[8]	20 mths	20 mths	28 mths	35 mths	0.23				
Hou 2007[9]*	---	---	47 mths	46 mths	---				
Milam 2007[10]	---	---	39 mths	48 mths	NS				
Silins 2007[11]	---	---	31 mths**	15 mths**					
Angioli 2006[13]*	22 mths	22 mths	87%	60%	0.02				
Lee 2006[20]	23 mths	20 mths	55 mths	53 mths	0.61				
Everett 2006[21]	---	---	42 mths	33 mths	0.3				
Inciura 2006[22]	---	---	25 mths	24 mths	0.131				
Steed 2006[17]*	36 mths	34 mths	44 mths	29 mths	---	3 yrs	53%	30%	0.03
Brunisholz 2005[15]	12 mths	30 mths	---	---	---	2 yrs 5 yrs	worse similar	better similar	0.042 NS
Hegazy 2005[23]*	---	---	28 mths	25 mths	0.5				
Loizzi 2005[18]*	34 mths	34 mths	40 mths	32 mths	0.66	3 yrs	50%	44%	0.66
Morice 2003[19]	---	---	22mths	26mths	NS	2yrs	52%	66%	NS
Fanfani 2003[24]*	37 mths	21 mths	44 deaths (40%)	32 deaths (44%)	---				
Ursic Vrscaj 2002[25]	---	---	26 mths	25 mths	0.79				
Ushijima 2002[26]*	---	---	23 mths	27 mths	NS				
Kayikciog Lu 2001[16]	27 mths	38 mths	25 mths	18 mths	---	5 yrs	24%	30%	0.9
Kuhn 2001[27]	19 mths	18 mths	23 mths	42 mths	0.007				
Schwartz 1999[28]*	26 mths	13 mths	26 mths	13 mths	0.16				

NAC–neoadjuvant chemotherapy; NS–not significant; PS–primary surgery

* These data include neoadjuvant patients who did not go on to have surgery.

** These data relate to median cancer-specific survival.

Trials published after Bristow review

Median overall survival in these trials ranged from 15 to 48 months in the NAC arms and 28 to 47 months in the control arms.

At a median follow-up of 41 months, the RCT[7] reported shorter median survival in the NAC arm compared to the control arm (29 vs 42 months) however, this difference was not statistically significant (p=0.07).

Of the level III trials, three reported similar median overall survival between treatment arms,[8-10] one trial reported lower median overall survival in the NAC arm compared to the control arm,[13] one trial reported shorter median cancer-specific survival in the NAC arm compared to the control arm[11] and one trial did not report on survival.[12] The trial that reported significantly inferior overall survival in the neoadjuvant arm included some patients who did not go on to receive surgery after primary chemotherapy.[13]

PROGRESSION-FREE AND DISEASE-FREE SURVIVAL

Trials reported either progression-free or disease-free survival outcomes (reported here as defined by trials, definitions of progression-free and/or disease-free survival for each trial were poorly reported) (see Table 3).

Eight trials reported no significant differences between treatment arms for progression-free or disease-free survival.[7,10,14,18-20,22,23] Two trials reported a statistically significant decrease in progression-free or disease-free survival,[13,17] these trials included data from patients in the neoadjuvant who did not go on to receive surgery (chemotherapy only). Five trials did not report on statistical significance.[9,13,16,24,26]

Table 3. Progression-free or disease-free survival

Trial	PS	NAC	p-value
Median progression-free survival			
Hou 2007[9]*	14 mths	16 mths	---
Milam 2007[10]	14 mths	20 mths	NS
Angioli 2006[13]*	10 mths	6 mths	---
Inciura 2006[22]	15 mths	13.3 mths	0.078
Steed 2006[17]*	22 mths	14 mths	0.04
Fanfani 2003[24]*	65 progressions (59%)	49 progressions (67%)	---
Ushijima 2002[26]*	65.1% remission	68.9% remission	---
Median disease-free survival			
Kumar 2007[7]	20 mths	25 mths	0.11
Lee 2006[20]	17 mths	15 mths	0.48
Bidzinski 2005[14]	19 mths	i) 20 mths, ii) 15 mths**	0.27
Hegazy 2005[23]*	19 mths	22 mths	0.4
Loizzi 2005[18]*	16 mths	21 mths	0.25
Morice 2003[19]	2yr: 25% disease-free	2yr: 26% disease-free	NS
Kayikciog Lu 2001[16]	12 mths	13.9 mths	---
Angioli 2006[13]*	49% disease-free	27% disease-free	0.01

NAC–neoadjuvant chemotherapy; NS–not significant; PS– primary surgery
* These data includes neoadjuvant patients who did not go on to have surgery.
** This trial has two neoadjuvant arms, the first had surgery after three cycles of chemotherapy, and the second had surgery after six cycles.

Silins *et al* reported that the hazard ratio (HR) for relapse was significantly higher in the NAC group compared to the PS group (HR: 1.69, 95% CI: 1.12, 2.55).[11]

Steed *et al* compared a subset survival analysis of only NAC patients who had surgery and PS patients (28 matched pairs) and found there was no progression-free survival difference between the groups (HR: 1.19; 95% CI: 0.60, 2.37; p=0.61).[17]

OPTIMAL CYTOREDUCTION

Optimal cytoreduction was defined differently between the trials, as no residual tumour, residual tumour ≤ 1cm, or residual tumour ≤ 2cm. The percentage of patients who received optimal cytoreduction varied between trials. The majority of the trials found that patients in the neoadjuvant treatment arms reported higher rates of optimal cytoreduction than those in the control arms, regardless of how optimal cytoreduction was defined, see Table 4. Two trials reported higher rates of optimal cytoreduction in the PS arm compared to the NAC arm.[13,22]

Table 4. Optimal cytoreduction

Trial	PS (%)	NAC (%)	p-value
Optimal cytoreduction defined as no residual tumour			
Angioli 2006[13]	96	80	
Steed 2006[17]	13	25	0.001
Kayikciog Lu 2001[16]	13.9	48.9	<0.001
Optimal cytoreduction defined as residual tumour ≤1cm			
Hou 2007[9]	71	95	<0.001
Milam 2007[10]	55	79	0.02
Silins 2007[11]	31.9	47.1	---
Giannopoulos 2006[12]	62.1	82.9	0.061
Everett 2006[21]	54	85.7	<0.001
Steed 2006[17]	27	73	0.001
Bidzinski 2005[14]	35.4	i) 79, ii) 84*	<0.001
Hegazy 2005[23]	62.5	72.2	0.5
Loizzi 2005[18]	60	76	0.67
Optimal cytoreduction defined as residual tumour ≤2cm			
Lee 2006[20]	45.5	77.8	0.04
Steed 2006[17]	49	73	0.001
Inciura 2006[22]	67	63	---
Brunisholz 2005[15]	71.4	88.9	---
Morice 2003[19]	94	94	NS
Kuhn 2001[27]	63	84	0.04
Optimal cytoreduction not defined			
Kumar 2007[7]		higher	<0.0001

NAC–neoadjuvant chemotherapy; NS–not significant; PS–primary surgery

*This trial has two neoadjuvant arms, the first had surgery after three cycles of chemotherapy, and the second had surgery after six cycles

MORBIDITY

Trials reported a range of morbidity outcomes. The most commonly reported outcomes are discussed. Morbidity outcomes reported relate to surgical morbidity. Data from the neoadjuvant group are only from patients who received surgery after chemotherapy, not chemotherapy alone.

Blood loss and transfusions

Thirteen trials reported data on blood loss and transfusions, see Table 5. Patients who received neoadjuvant chemotherapy before surgery reported significantly lower amounts of blood loss (median blood loss range: 373–806 ml) compared to primary surgery (median blood loss range: 400–1200 ml). Transfusions were needed in 18–43% of NAC patients and in 33–57% of PS patients. Two of four trials that reported on transfusions found the NAC group to have a significantly lower percentage of patients requiring transfusion,[10,19] the remaining two did not find the difference between NAC and PS significantly different.[9,21]

Operation time

The majority of trials that report on operation time found that patients who received neoadjuvant chemotherapy spent shorter time in surgery (10–65 minutes less), however this was often not statistically significant, see Table 6. Overall, operation time ranged from 95 to 260 minutes in the NAC arms and 110–276 minutes in control arms.

Days in hospital

The majority of trials also reported a shorter stay in hospital in patients who received neoadjuvant chemotherapy compared to those who had primary surgery, see Table 6. While NAC patients stayed in hospital for a median 4–12 days, PS patients stayed for a median 5–20 days, the

difference between the NAC and PS arms ranged from 0 to 8 days, with an average of three days.

Admission and time spent in intensive care

Only six trials reported on admission and/or time spent in the intensive care unit (ICU), of these four found NAC patients to have lower rates of ICU admission and/or shorter stays in ICU,[12,19,23,28] see Table 6. The other two trials found no significant difference between NAC and PS patients for admission to or time spend in ICU.[9,21]

Table 5. Blood loss and transfusions

Trial, Year	Median blood loss (ml)			Transfusion needed (%)			Mean transfusion units*		
	PS	*NAC*	*p-value*	*PS*	*NAC*	*p-value*	*PS*	*NAC*	*p-value*
Kumar 2007[7]	520	373	<0.003	---	---	---	---	---	---
Hou 2007[9]	1033	546	<0.0001	56.7	42.6	NS	2.43	1.21	0.03
Milam 2007[10]	1139	640	0.006	51	28	0.03	---	---	---
Giannopoulos 2006[12]	1000	500	0.043	---	---	---	---	---	---
Angioli 2006[13]	600	500	---	---	---	---	---	---	---
Lee 2006[20]	1061	620	0.04	---	---	---	---	---	---
Everett 2006[21]	400	400	0.237	33.3	41.8	0.214	2.47	3.02	0.74
Brunisholz 2005[15]	1200	600	---	---	---	---	2.5	0	---
Hegazy 2005[23]	735	420	0.02	---	---	---	---	---	---
Morice 2003[19]	---	---	---	56	18	<0.001	---	---	---
Ushijima 2002[26]	1159g (1093ml)**	854g (806ml)**	NS	---	---	---	742ml	532ml	<0.05
Kuhn 2001[27]	---	---	---	---	---	---	2	2	NS
Schwartz 1999[28]	1000	600	0.001	---	---	---	---	---	---

NAC–neoadjuvant chemotherapy; NS–not significant; PS–primary surgery
* 1 unit = 300 – 500 mL
** Average blood density = 1.06 g/ml

Table 6. Operation/surgery-related outcomes

Trial	Operation time (min)			Days in Hospital			ICU admission (%)			Days in ICU		
	PS	*NAC*	*p-value*	*PS*	*NAC*	*p-value*	*PS*	*NAC*	*p-value*	*PS*	*NAC*	*p-value*
Kumar 2007[7]	110	95	0.12	12	9.4	0.1	---	---	---	---	---	---
Hou 2007[9]	276	211	<0.0001	8.5	5.7	<0.0001	14.4	10	NS	1.6	2	NS
Milam 2007[10]	220	209	NS	10	6	<0.001	---	---	---	---	---	---
Giannopoulos 2006[12]	---	---	---	8	7	0.005	48.3	5.7	<0.001	---	---	---
Angioli 2006[13]	170	115	---	5	4	---	---	---	---	---	---	---
Lee 2006[20]	---	---	---	10.4	9.7	---	---	---	---	---	---	---
Everett 2006[21]	181	195	0.055	6	6	0.131	5.9	6.1	0.94	1.8	1.5	0.70
Brunisholz 2005[15]	185	130	---	---	---	---	---	---	---	---	---	---
Hegazy 2005[23]	190	150	NS	15.9	10.5	0.05	---	---	---	4.4	1.7	0.03
Morice 2003[19]	---	---	---	20	12	<0.001	12	4	0.02	---	---	---
Ushijima 2002[26]	201	238	<0.05	---	---	---	---	---	---	---	---	---
Kuhn 2001[27]	270	260	NS	---	---	---	---	---	---	---	---	---
Schwartz 1999[28]	---	---	---	11	7	<0.001	---	---	---	1.3	1.0	0.01

ICU – intensive care unit; NAC – neoadjuvant chemotherapy; NS – not significant; PS – primary surgery

Intra-operative and post-operative complications

Only three trials reported on intra-operative complications,[10,13,21] with no significant difference observed between NAC or PS patients, see Table 7.

Post-operative complications were mainly reported separately. Five trials reported overall rates of post-operative complications between 4% and 62%,[9,10,13,19,21] with higher rates seen in the PS arms (although only one trial reported the difference as statistically significant[19]), see Table 7. As the complications reported between trials varied, only the most commonly reported outcomes will be discussed.

Five trials reported on deep venous thrombosis[12,21,23]/thromboembolism,[9,27] with low rates (1–9%) seen in the NAC and PS groups (no significant difference observed between treatment groups).

Four trials reported on bowel surgery, with three trials finding no significant difference between treatment groups.[12,20,21] These trials reported rates of bowel surgery ranging from 6% to 17%. One trial reported a significantly higher rate of bowel surgery in the control group compared to the NAC group (73% vs 18%, p<0.001).[19]

No significant difference was seen for bowel and/or bladder injury between treatment groups.[9,12,21] Reported rates of bowel and/or bladder injury ranged from 0% to 14%.

Table 7. Intra- and post-operative complications

Trial	Intra-operative complications (%)			Post-operative complications (%)		
	PS	*NAC*	*p-value*	*PS*	*NAC*	*p-value*
Hou 2007[9]	---	---	---	33.9	27.8	NS
Milam 2007[10]	4	7	NS	10	4	NS
Angioli 2006[13]	6	4	---	9	4	---
Everett 2006[21]	14.7	17.3	0.611	61.8	59.2	0.709
Morice 2003[19]	---	---	---	53	12	<0.001

NAC–neoadjuvant chemotherapy; NS–not significant; PS–primary surgery

ADVERSE EVENTS

Information on adverse events was limited. The RCT by Kumar *et al*[7] reported that there were no significant differences in grade III/IV gastrointestinal (GIT) or bone marrow toxicity between treatment arms.

QUALITY OF LIFE

Information on quality of life (QoL) outcomes was limited. The RCT by Kumar *et al*[7] used the validated Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire to measure QoL. This trial reported that patients in the neoadjuvant group had a statistically significant higher score (i.e. better quality of life) at the end of treatment compared to those in the control arm (114 vs 93; p<0.001).

INTERVAL CYTOREDUCTION

While trials on interval surgical cytoreduction were excluded from the NBOCC review, the systematic review by Bristow[4] did include some information on these trials. Of three prospective randomised trials[29-31] and six non-randomised trials,[32-37] which were included in the Bristow review, only one of the RCTs[30] reported a statistically significant improvement in survival in the interval surgery group compared to those who did not have interval surgery. The remaining trials found no survival difference between the groups. Complications from interval debulking are similar to those experienced after primary surgery (bowel/bladder injury, blood loss, fever and infection).

SUBGROUP ANALYSES

Some of the trials investigated the difference between subgroups, such as comparing those who achieved optimal cytoreduction to those who did not, stage IIIC compared to stage IV disease, use of taxanes, and age (<65 yrs compared to >65 yrs). Subgroup analyses were often reported for overall or progression-free survival.

Optimal cytoreduction

Patients who underwent optimal cytoreduction (as defined by individual trials) had longer median survival compared to those who had suboptimal cytoreduction, see Table 8. This was true when comparing all patients who were optimally cytoreduced with those who had suboptimal cytoreduction (irrespective of original treatment groups) and when stratifying by cytoreduction outcome within treatment groups.

Table 8. Survival outcomes by optimal cytoreduction

Trial	Subgroup	Median overall survival			Progression-free survival		
		PS	*NAC*	*p-value*	*PS*	*NAC*	*p-value*
Everett 2006[21]	Optimal cytoreduction	42 mths		0.031	21 mths	16 mths	<0.001 between all four groups
	Suboptimal cytoreduction	34 mths			11 mths	7 mths	
Lee 2006[20]	Optimal cytoreduction	53 mths		NR			
	Suboptimal cytoreduction	12 mths					
Fanfani 2003[24]	Optimal cytoreduction, 0 cm	Not reached	Not reached	PS arm: 0.001; NAC arm: NS	86 mths	22 mths	PS arm: 0.007; NAC arm: NS
	Suboptimal cytoreduction, <2 cm	54 mths	27 mths		20 mths	18 mths	
Shibata 2003[38]	Optimal cytoreduction, <2 cm	NR	Longer	0.03			
	Suboptimal cytoreduction, >2 cm	NR	Shorter				
Ursic Vrscaj 2002[25]	Optimal cytoreduction, 0 cm	Longer	Longer	PS arm: 0.002; NAC arm: 0.01			
	Suboptimal cytoreduction, >1 cm	Shorter	Shorter				
Ushijima 2002[26]	No residual disease		35 mths				
	Residual <1cm		22 mths				
	Residual >1cm		25 mths				
Schwartz 1999[28]	Optimal cytoreduction	NR	Longer	<0.001			
	Suboptimal cytoreduction	NR	Shorter				
Comparison of patients receiving optimal cytoreduction							
Hou 2007[9]	Optimal cytoreduction	NR	NR	0.124	NR	NR	0.69
Angioli 2006[13]	Optimal cytoreduction	86%	81%	NS			
Inciura 2006[22]	Optimal cytoreduction	NR	NR	0.065	NR	NR	0.094
Loizzi 2005[18]	Optimal cytoreduction	40	48	0.38			

NAC–neoadjuvant chemotherapy; NR–not reported; NS–not significant; PS–primary surgery

When analysing patients who had achieved optimal cytoreduction only, no difference in survival was observed between NAC and PS groups,[9,13,18,22] see Table 8.

Silins *et al*[11] reported the incidence of disease-related death was significantly higher in suboptimally treated patients (suboptimal debulking surgery and/or suboptimal chemotherapy) (HR:1.50; 95% CI: 1.03, 2.19).

Stage of disease

Patients with stage IIIC disease appeared to have longer overall and progression-free survival compared to patients with stage IV disease,[9,18,22,28] see Table 9. The difference in survival between treatment arms when comparing patients of the same stage was not statistically significant.

Table 9. Survival outcomes by stage of disease

Trial	Subgroup	Median overall survival (months)			Progression-free survival (months)		
		PS	*NAC*	*p-value*	*PS*	*NAC*	*p-value*
Hou 2007[9]	Stage IIIC	45	45*		17	18*	
	Stage IV	20	31**		9	15**	
Inciura 2006[22]	Stage III	29.3	25.9	0.25	17.5	15.7	0.13
	Stage IV	14.9	15.4	0.61	8.2	8.7	0.18
Loizzi 2005[18]	Stage III	40	32	0.57			
	Stage IV	36	34	0.84			
Schwartz 1999[28]	Stage IIIC	30		0.009			
	Stage IV	13					

NAC–neoadjuvant chemotherapy; PS–primary surgery
* Patients in this group classified as having intra-abdominal disease.
** Patients in this group classified as having extra-abdominal disease.

Age

Based on this review, the effect of age on overall survival is unclear. Multivariate analyses by Inciura *et al*[22](<65yrs) and Kuhn *et al*[27] (≤62.5yrs) found age to be a significant independent predictor of survival. However, Schwartz *et al* (1999)[28] reported that within treatment arms, there was no difference in survival for those less than 65 years compared to older than 65 years, see Table 10. No further trials reported age as a predictor of survival (either not statistically significant or not reported at all).

Table 10. Survival outcome by age

Trial	Subgroup	Median overall survival (months)		
		PS	*NAC*	*p-value*
Schwartz 1999[28]	≤65	29	12	0.88
	>65	18	14	0.32
	p-value	0.73	0.24	-

NAC – neoadjuvant chemotherapy; PS – primary surgery

Taxane-containing chemotherapy

Hou *et al*[9] stratified results by whether taxanes were included in the chemotherapy regimen. Improved survival was reported in NAC patients who received a taxane (carboplatin/paclitaxel) compared to NAC patients who did not receive a taxane (carboplatin/cyclophosphamide) (p=0.008). This study also reported that NAC patients who received the taxane containing regimen had a higher estimated blood loss due to surgery compared to those who did not receive a taxane (621 ml vs 440 ml, p=0.047).

Ushijima *et al*[26] reported that regimens containing taxane and platinum showed a higher response for NAC and a higher rate of optimal reduction (<1cm, 75%) and a higher rate of remission (71.4%) compared to other platinum regimens.

Cycles of chemotherapy

Two trials reported on the effect of number of cycles/courses of neoadjuvant chemotherapy on survival.[14,18] While shorter survival times were observed with increasing cycles of chemotherapy, the difference was not statistically significant, see Table 11.

Table 11. Survival outcomes by cycles of neoadjuvant chemotherapy

Trial	Subgroup	Overall survival		Disease-free survival	
		NAC	*p-value*	*NAC*	*p-value*
Bidzinski 2005[14]	3 cycles NAC			20 mths	0.27
	6 cycles NAC			15 mths	
Loizzi 2005[18]	≤ 3 courses NAC	34 mths	0.74		
	> 3 courses	25 mths			

NAC – neoadjuvant chemotherapy

Dose of chemotherapy

One trial reported on the effects of different doses of chemotherapy on overall survival.[38] Shibata *et al* reported patients who received ≥18mg/m2/week of cisplatin in NAC had longer survival than those receiving <18mg/m2/week (p=0.01).[38]

Patients receiving neoadjuvant chemotherapy but no surgery

Some patients assigned to the neoadjuvant chemotherapy arm did not go on to have surgery, mainly due to being unresponsive to chemotherapy, showing progression of disease or being considered unable to have surgery because of co-morbidities. Four trials reported that these patients had significantly lower overall survival than patients treated by neoadjuvant chemotherapy followed by surgery,[24,26,28,38] see Table 12. Only one trial reported on progression-free survival, with shorter median time to progression in NAC patients who did not have surgery compared to those who did (8 vs 22 months, p=0.00001).[24]

Table 12. Overall and progression-free survival of neoadjuvant chemotherapy patients

Trial	Number of patients		Overall survival (months)			Progression-free survival (months)		
	NAC no surgery	*NAC with surgery*	*NAC no surgery*	*NAC with surgery*	*p-value*	*NAC no surgery*	*NAC with surgery*	*p-value*
Fanfani 2003[24]	10	63	14	40	0.0001	8	22	0.00001
Shibata 2003[38]	10	19	Shorter	Longer	<0.01			
Ushijima 2002[26]	20*	45	10.4	26.5	<0.01			
Schwartz 1999[28]	18	41	8	18	0.0001			

NAC – neoadjuvant chemotherapy
*two patients did not receive any chemotherapy

ONGOING CLINICAL TRIALS

The following clinical trials websites were searched to identify any additional studies investigating NAC in ovarian cancer that have not yet reported:

- Australian Clinical Trials Registry http://www.actr.org.au/
- Clinical Trials.gov http://www.clinicaltrials.gov/
- Current Controlled Trials http://www.controlled-trials.com/
- National Research Register http://www.nrr.nhs.uk/
- National Cancer Institute http://www.cancer.gov/clinicaltrials.

Two randomised controlled trials were identified,[39,40] see Table 13. Both trials include patients with ovarian, peritoneal or fallopian tube cancers. The EORTC-55971 trial[39] has recently closed; however, the CHORUS trial[40] is still recruiting participants. It is unknown when these trials are likely to report results.

Table 13. Ongoing studies investigating neoadjuvant chemotherapy

Title	Location/s	Participants	Treatment	Objectives
Phase III Randomized Study of Neoadjuvant Chemotherapy Followed By Interval Debulking Surgery Versus Upfront Cytoreductive Surgery Followed By Chemotherapy With or Without Interval Debulking Surgery in Patients With Stage IIIC or IV Ovarian Epithelial, Peritoneal, or Fallopian Tube Cancer				
EORTC-55971 NCT00003636[39] Trial started: 1998 Recruitment closed: Dec 2006	Europe	Stage IIIC or IV ovarian epithelial, peritoneal or fallopian tube carcinoma N = 704 patients	**Arm I**. Neoadjuvant chemotherapy followed by interval debulking surgery followed by further chemotherapy **Arm II**. Upfront cytoreductive surgery followed by chemotherapy with or without interval debulking surgery	i. compare the overall survival and progression free survival ii. compare QoL iii. compare the different treatment complications
Phase II/III Randomized Pilot Study of the Timing of Surgery and Chemotherapy in Patients With Newly Diagnosed Advanced Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cavity Cancer				
RCOG-MRC-**CHORUS** NCT00075712[40] Trial started: 2003 Recruitment ongoing	UK	Women 18 yrs and over with newly diagnosed advanced ovarian epithelial, primary peritoneal or fallopian tube cancer Projected accrual: 150 patients	**Arm I**. Neoadjuvant chemotherapy followed by radical surgery followed by further chemotherapy **Arm II**. Radical surgery followed by chemotherapy	Determine the impact of the timing of surgery and chemotherapy in patients Outcomes: i. Overall and progression-free survival ii. Quality of life

DISCUSSION

The majority of the trials included in the NBOCC review, and in the previous Bristow review,[4] are considered level III evidence, therefore it is difficult to draw firm conclusions on the use of neoadjuvant chemotherapy for the treatment of ovarian cancer compared to primary surgery.

Many of the studies are affected by selection bias as the populations selected to be in the neoadjuvant arms of these trials were patients unsuitable for primary surgery. These patients were likely to have a poorer outcome compared to patients in the primary surgery group. This was reflected in unbalanced patient characteristics, such as older age and greater percentages of stage IV disease in patients in the NAC arms. The meta-analysis by Bristow and Chi[5] indicated that higher proportions of stage IV disease are associated with decreases in median survival time but that age was not associated with differences in survival.

All chemotherapy regimens investigated in the trials contained a platinum compound (carboplatin or cisplatin). A combination of platinum and taxane chemotherapy is considered the gold standard for treatment of advanced ovarian cancer.[2] Not all patients in the trials received a taxane (docetaxel or paclitaxel) in their chemotherapy regimen; however, the rates of taxane use were reported in the trials. Most trials incorporated similar rates of taxane use in the neoadjuvant chemotherapy and the primary surgery arms. Higher rates of taxane use were reported in the more recently published trials, reflecting changes in practice over time. The meta-analysis by Bristow and Chi[5] found that overall survival increased as rates of taxane use increased. For trials that compared a neoadjuvant arm to an historic control arm, results may be confounded by higher amounts of taxane therapy in the neoadjuvant arm treatments, stage migration and/or improved quality of supportive care leading to improved outcomes in the neoadjuvant arm.

At this stage, the question of the effect of neoadjuvant chemotherapy on overall survival, compared to primary surgery, is unanswerable. The trials included in this review were often underpowered to detect an overall survival difference, with small patient numbers and/or limited follow-up. Some trials reported shorter median survival in NAC arms; however, the difference was often not statistically significant. Longer follow-up is needed from the Kumar RCT[7] as well as results from the larger RCTs yet to report (EORTC,[39] CHORUS[40]) to determine the effects of neoadjuvant chemotherapy on survival, compared to primary surgery.

In trials that compared patients who had NAC to those who had suboptimal surgery, not those who had the 'gold standard' of optimal cytoreduction, it was expected that survival outcomes in the neoadjuvant chemotherapy group would compare favourably to the control group.

Optimal cytoreduction was consistently reported as an independent predictor of improved overall survival. This effect was seen when comparing all patients with optimal cytoreduction with patients who had suboptimal cytoreduction (irrespective of treatment group) and within treatment groups. When comparing only patients who had optimal cytoreduction, no difference in overall survival was reported between PS and NAC groups. Everett *et al*[21] reported that patients who had been optimally cytoreduced in the PS group had longer progression-free survival than patients who were optimally cytoreduced in the NAC group (21 vs 16 months, $p<0.001$).

In some trials, not all patients assigned to the neoadjuvant chemotherapy arms went on to receive cytoreductive surgery. Often only those who responded to chemotherapy progressed to receive surgery, therefore only the patients with a better prognosis from the neoadjuvant group were compared to the primary surgery group (depending on how the trial conducted their

analysis, e.g. intention-to-treat). Subgroup analyses indicated that patients in the NAC arm who did not receive surgery had poorer survival than those who had NAC followed by surgery. This result is expected due to these patients representing a poorer prognosis group, with reasons for not having surgery including progression of disease. The NBCC's* guidelines state that surgery has no place for women who develop progressive disease during their initial chemotherapy program.[2]

Based on the studies in this review, it is unclear whether neoadjuvant chemotherapy had an effect on progression-free survival compared to primary surgery. Most trials showed no significant difference between progression-free and/or disease-free survival between the two treatment groups.

Treatment with neoadjuvant chemotherapy increased the rates of optimal cytoreduction achieved at surgery. Trial definitions of optimal cytoreduction varied from no visible residual disease to residual tumour size ≤2cm.

Surgical morbidity outcomes appear to be better in the groups treated with neoadjuvant chemotherapy than those treated with primary surgery. Patients in the NAC arms reported lower estimated blood loss and less time in hospital than those in the PS arms. The differences between the groups for operation time, ICU admission, intra-operative and post-operative complications were often not significant.

Adverse events and QoL were poorly reported in the trials. This may be due to the retrospective nature of the trials and difficulty with recall and confirmation of these outcomes.

There are limitations in this review and the identified trials. Overall, it is difficult to draw firm conclusion on the benefits and harms of neoadjuvant chemotherapy compared to primary surgery. All but one of the reported trials are classified as level III evidence and, as such, are subject to bias, which may influence the trial outcomes. Also, there were difficulties in comparing the trials due to the variations in trial protocols and reported outcomes. Chemotherapy regimens differed greatly between trials, including varying rates of taxane use. Trials classified 'unresectable' patients differently, procedures used to determine 'unresectability' varied from expert opinion from the surgical team to set defined criteria, including spread of disease. Definitions of optimal cytoreduction varied between trials from no visible residual disease to residual tumour size <2cm.

Further clinical trial information is needed to clarify the benefits and harms of neoadjuvant chemotherapy. Results from the prospective randomised controlled trials that are currently in progress are needed to determine the optimal role, and the impact on survival, of neoadjuvant chemotherapy in the treatment of women with ovarian cancer and extra-ovarian disease. While surgical morbidity appears to be improved by use of neoadjuvant chemotherapy before surgery, QoL data are needed to assess the psychosocial impacts of neoadjuvant chemotherapy compared to primary surgery. Also, a standard classification to determine which patients are eligible to receive neoadjuvant chemotherapy needs to be established.

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* *In February 2008, National Breast Cancer Centre (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC).*

CONCLUSIONS

Data from 26 articles in this review do not provide clear evidence for the use of neoadjuvant chemotherapy for women with ovarian cancer, compared to primary surgery. The effects on both overall and progression-free survival are unclear. The only consistently reported predictor of improved survival in the trials was optimal cytoreduction. It appears that compared to primary surgery, patients given chemotherapy before surgery report better surgical morbidity outcomes, including lower blood loss and shorter hospital stay.

While limited data suggest that rates of adverse events are low and similar between neoadjuvant chemotherapy and primary surgery arms, adverse events are poorly reported in current trials, as are QoL outcomes. Limited data suggest that quality of life is improved in patients receiving neoadjuvant chemotherapy compared to those treated with primary surgery.

Longer follow-up and results of ongoing randomised controlled trials are needed and are awaited with interest. Further research, including the possible initiation of a collaborative Australian trial, may be warranted.

Based on the evidence presented in this review, no changes to current clinical practice guidelines are recommended.

APPENDICES

Appendix 1. Literature databases searched

Source	Results/Retrievals
Medline (Ovid)	177
CINAHL (Ovid)	9
EBM Reviews (Ovid)	18
Embase	124
Pubmed	302
Additional Papers (sourced from reference lists and conference sites)	5

Appendix 2. Health technology assessment, guidelines and clinical trials websites searched

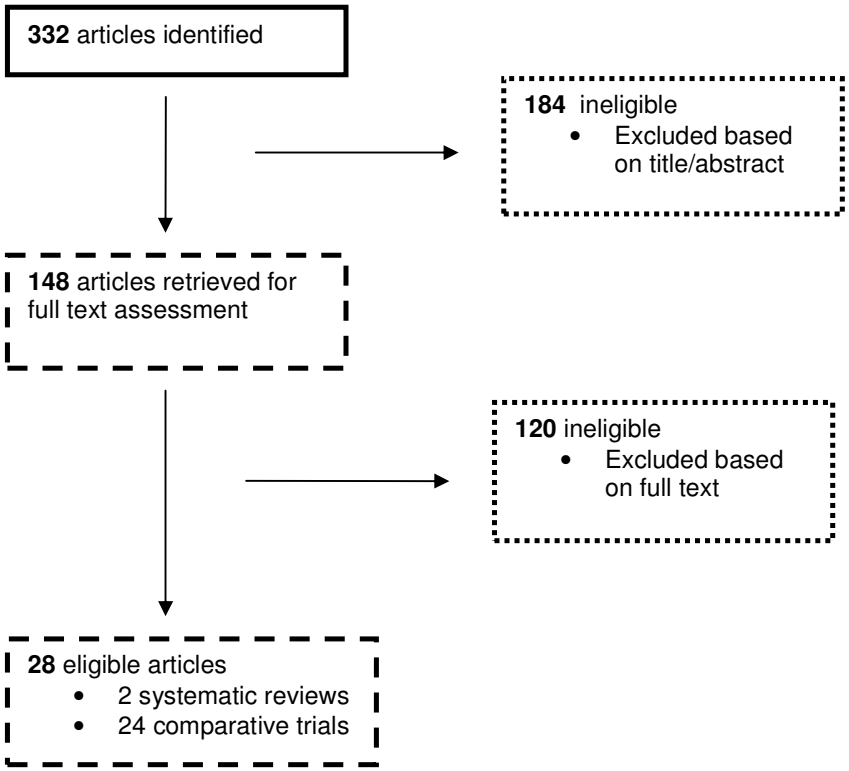
Country	Acronym	Organisation	Website
Australia	ACTR	Australian Clinical Trials Registry	http://www.actr.org.au/
	NICT	National Institute of Clinical Trials	http://www.nhmrc.gov.au/nics/asp/index.asp?
Canada	CCO	Cancer Care Ontario	http://www.cancercare.on.ca/
International	HTAi	Health Technology Assessment International	http://www.htai.org/
Scotland	SIGN	Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
UK	CRD	Centre for Reviews and Dissemination	http://www.york.ac.uk/inst/crd/
	CCT	Current Controlled Trials	http://www.controlled-trials.com/
	NICE	National Institute for Health and Clinical Excellence	http://www.nice.org.uk/
	NRR	National Research Register	http://www.nrr.nhs.uk/
US		ClinicalTrials.gov	http://www.clinicaltrials.gov/
	NCI	National Cancer Institute Clinical Trials	http://www.cancer.gov/clinicaltrials
	NGC	National Guideline Clearinghouse	http://www.guideline.gov/

Appendix 3. Terms used in search strategy

Key areas	Search terms
Ovarian cancer and extra-ovarian disease	(ovarian neoplasms/ or ovarian cancer or peritoneal neoplasms or peritoneal cancer or extra?ovarian))
Neoadjuvant chemotherapy	((neoadjuvant therapy/ or neo?adjuvant therapy) or (neo?adj$ and chemotherapy$) or (interval debulking)

/ indicates Mesh terms, $ or ? indicates truncated terms.

Appendix 4. Flowchart of inclusion/exclusion process



Appendix 5. NHMRC Levels of Evidence[3]

Table 1.3 Designation of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pretest/post-test.

Source: NHMRC 1999

Appendix 6 Characteristics of comparative trials included in Bristow systematic review[4] and NBOCC review (certain trials and case-series' excluded).

Study	Treatment	FIGO stage	n	Follow-up	Platinum based chemotherapy	Taxane use	Cycles prior to interval surgery
Lee 2006[20]	NAC	IIIC: 88.9% IV: 11.1%	18	20 mths	100%	100%	3
	PS	IIIC: 90.9% IV: 9.1%	22	22.5 mths	100%	100%	NA
Everett 2006[21]	NAC	III:73.5% IV: 26.5%	98		100%	94%	3
	PS	III: 92.2% IV: 7.8%	102		100%	94%	NA
Inciura 2006[22]	NAC	III: 77.5% IV: 22.5%	213		100%	0%	3
	PS	III: 84.5% IV: 15.5%	361		100%	0%	NA
Steed 2006[17]	NAC	III: 68% IV: 32%	50	34 mths	100%	98%	3 or 4
	PS	III: 92.4% IV: 7.6%	66	36 mths	100%	94%	NA
Hegazy 2005[23]	NAC	IIIC: 40.7% IV: 59.3%	27		100%	0%	3
	PS	IIIC: 43.8% IV: 56.2%	32		100%	0%	NA
Loizzi 2005[18]	NAC	IIIC: 76.7% IV: 23.3%	30	34 mths	100%	60%	4.1
	PS	IIIC: 76.7% IV: 23.3%	30	34 mths	100%	NR	NA
Morice 2003[19]	NAC	IIIC:88.2% IV: 11.8%	34		100%	94.1%	3
	PS	IIIC:88.2% IV: 11.8%	34		100%	0%	NA
Shibata 2003[38]	NAC	III: 82.8% IV: 17.2%	29		100%	0%	6
	PS	III: 86.5% IV: 13.5%	96		100%	0%	NA
Fanfani 2003[24]	NAC	IIIC: 100%	73	21 mths	100%	57.5%	3
	PS	IIIC: 100%	111	37 mths	100%	NR	NA
Ursic Vrscaj 2002[25]	NAC	IIIC: 85% IV: 15%	20		100%	0%	3 to 5
	PS	IIIC: 87.3% IV: 12.7%	55		100%	0%	NA
Ushijima 2002[26]	NAC	IIIC: 78.5% IV: 21.5%	65		100%	21.5%	4
	PS	IIIC: 77.8% IV: 22.2%	63		10%	NR	NA
Kayikciog Lu 2001[16]	NAC	IIIC: 46.7% IV: 53.3%	45	38 mths		15.3%	3
	PS	IIIC: 64.6% IV: 35.4%	158	27 mths		38.4%	NA
Kuhn 2001[27]	NAC	IIIC: 100%	31	18 mths	100%	NR	3
	PS	IIIC: 100%	32	19 mths	100%	NR	NA
Schwartz 1999[28]	NAC	III: 32% IV: 68%	56	13 mths	100%	8.5%	5
	PS	III: 80.4% IV: 19.6%	206	26 mths	100%	0%	NA
Vergote 1998[41]	NAC	III: 59% IV: 41%	75	24 mths	92%	20%	
	PS	III: 88% IV: 11%	98	24 mths	91%	19%	NA

NA–not applicable; NAC–neoadjuvant chemotherapy; NR– not reported; PS–primary surgery

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