

OVARIAN CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

APPENDIX



OVARIAN CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

APPENDIX

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1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Composition of the Guideline Development Group

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Vincent Van de Caveye	Radiologist, Universitair ziekenhuis Gasthuisberg, Leuven
Geert Villeirs	Radiologist, Universitair ziekenhuis Gent, Gent
Peter Vuylsteke	Medical oncologist, Clinique et Maternité Sainte Elisabeth, Namur



1.2. Composition of the KCE expert team

KCE member	Specific role
Leen Verleye	Principal Investigator
Joan Vlayen	Senior Researcher
Nicolas Fairon	Information Specialist
Sabine Stordeur	Project Coordinator and Senior supervisor

1.3. External researchers involved in the guideline development

Subcontractor	Specific role
Rob Scholten	Senior clinical epidemiologist
Lotty Hooft	Senior clinical epidemiologist
Fleur van de Wetering	Researcher
Pauline Heus	Researcher
Jaap Hoogendam	Researcher
Johanna Damen	Researcher
Frederieke van der Baan	Researcher
Ronald Zweemer	Gynaecological oncologist



2. PICO RESEARCH QUESTIONS

2.1. Pre-operative assessment pelvic mass

PICO

Population	Adult patients (≥18 years of age) with a (complex) pelvic mass without clear signs of advanced disease
Intervention	RMI or other diagnostic tests/models
Comparator	No formal test/lodel, subjective assessment
Outcomes	Clinical outcomes Proportion of patients undergoing unnecessary laparotomy and/or staging (7.8) Overall survival (7.5) Disease-free survival (7.3) Quality-of-Life (5.8) Proportion of patients treated by a gynaecological oncologist (6.8) Proportion of patients who need two surgical procedures (5.1) Proportion of patients who need adjuvant chemotherapy (4.6) Diagnostic accuracy outcomes False negatives (9.0) True negatives (7.8) True positives (7.3) False positives (7.3) Adverse events associated with diagnostic intervention (5.5) Inconclusive results (5.2)



2.2. Intra-operative frozen section

PICO

Population	Adult patients (≥18 years of age) with (presumed) early-stage ovarian cancer
Intervention	Use of intraoperative frozen section
Comparator	No use of intraoperative frozen section
Outcomes	Clinical outcomes Proportion of patients undergoing unnecessary staging/lymphadenectomy (7.5) Proportion of patients who need two surgical procedures (7.4) Perioperative morbidity (6.9) Quality-of-Life (6.6) Overall survival (5.0) Disease-free survival (5.3) Diagnostic accuracy outcomes False positives (7.8) False negatives (7.3) Inconclusive results (6.8) True positives (6.3) True negatives (5.5) Adverse events associated with diagnostic intervention (5.5)



2.3. Lymphadenectomy

PICO

Population	Adult patients (≥ 18 years of age) with a) borderline, b) micro- invasive and c) invasive (presumed) early-stage ovarian cancer who underwent systematic pelvic and para-aortic lymphadenectomy
Intervention	NA
Comparator	NA
Outcomes	Prevalence of malignant disease in pelvic and para-aortic lymph nodes

2.4. Adjuvant chemotherapy

PICO

Population	Adult patients (≥ 18 years of age) with a) borderline, b) micro- invasive and c) invasive (presumed) early-stage ovarian cancer; subgroups according to patient, tumour or staging characteristics
Intervention	Adnexectomy + surgical staging with adjuvant chemotherapy
Comparator	Adnexectomy + surgical staging without adjuvant chemotherapy
Outcomes	Overall survival (8.0) Side-effects of treatment (7.8) Disease-free survival (7.5) Quality of life (7.4)



2.5. Laparoscopic surgery

PICO

Population	Adult patients (≥18 years of age) with presumed borderline or invasive early-stage ovarian cancer who undergo surgery, including comprehensive staging
Intervention	Bilateral salpingo-oophorectomy + comprehensive staging via laparoscopy (included in intervention group if conversion to laparotomy needed)
Comparator	Bilateral salpingo-oophorectomy + comprehensive staging via laparotomy (vertical incision)
Outcomes	Overall survival (7.5) Treatment-related morbidity (7.4) Quality of life (6.8) Disease-free survival (6.6) Proportion of patients who need adjuvant chemotherapy (6.1)

2.6. Laparoscopy, PET-CT and MRI to predict end result of cytoreductive surgery

PICO

Population	Adult patients (≥18 years of age) with advanced stage ovarian cancer (stage IIIC-IV), possibly eligible for debulking surgery based on CT-scan
Intervention	PET-CT, (diffusion) MRI or laparoscopy as add-on test
Comparator	CT alone
Outcomes	Clinical outcomes Overall survival (7.3) Quality-of-Life (6.6) Treatment morbidity/adverse events (6.2) Proportion of debulking procedures with end result > 1 cm (7.3) Diagnostic accuracy outcomes False negatives (8.0) True positives (7.4)

**PICO**

Inconclusive results (7.2)
False positives (7.1)
True negatives (7.0)
Adverse events associated with diagnostic intervention (6.5)

2.7. Aim of cytoreductive surgery: no macroscopic disease?**PICO 1**

Population	Adult patients (≥18 years of age) with advanced stage ovarian cancer (stage IIIc-IV)
Intervention	Complete debulking (no macroscopic disease left in situ)
Comparator	Debulking with end result a) macroscopic disease < 1 cm ('optimal') or b) macroscopic disease > 1 cm ('incomplete')
Outcomes	Overall survival (8.6) Quality of life (7.5) Peri-operative morbidity (6.9)

PICO 2

Population	Adult patients (≥18 years of age) with advanced stage ovarian cancer (stage IIIc-IV)
Intervention	Ultra-radical (extensive) surgery
Comparator	Standard surgery
Outcomes	Overall survival (8.6) Quality of life (7.5) Peri-operative morbidity (6.9)



2.8. Neoadjuvant chemotherapy

PICO	
Population	Adult women with advanced stage (IIIc/IV) ovarian cancer
Intervention	Primary debulking followed by chemotherapy
Comparator	Neoadjuvant chemotherapy followed by interval debulking
Outcomes	Overall survival Progression-free survival Adverse events Quality of life

2.9. Intra-peritoneal chemotherapy

PICO	
Population	Women with newly diagnosed stage III-IV ovarian cancer who had cytoreductive surgery to residual disease < 1 cm. Women who received preoperative neoadjuvant (IV) chemotherapy were not excluded.
Intervention	First-line chemotherapy that was at least partially administered intraperitoneally
Comparator	First-line chemotherapy that was administered exclusively intravenously
Outcomes	Treatment morbidity/adverse events (6.4) Quality-of-Life (6.3) Overall survival (5.8) Progression-free survival (5.4)

2.10. First-line weekly (dose dense) chemotherapy

PICO	
First-line dose-dense chemotherapy	
Population	Included: women with newly diagnosed stage II-IV epithelial ovarian cancer who underwent debulking surgery (primary debulking) or who are planned for interval debulking surgery. Studies who also include women with high risk early-stage ovarian EOC who underwent surgical staging will also be included.



PICO	First-line dose-dense chemotherapy
	Excluded: Studies that included (high risk) early-stage EOS only
Intervention	Included: dose-dense (weekly) chemotherapy, containing paclitaxel and carboplatin or cisplatin. Studies with dose-dense schedules for paclitaxel only or for both chemotherapy substances will be included. Excluded: studies comparing two 3-weekly schedules using different doses or different durations of infusion
Comparator	Included: 3-weekly schedules of paclitaxel and carboplatin or cisplatin. Excluded: treatment schedules including other chemotherapy substances or targeted therapy
Outcomes	Overall survival (7.1) Progression-free survival (6.0) Quality-of-life (6.9) Treatment morbidity/adverse events (6.9) CTCAE grade III-IV toxicity (6.9)

2.11. Routine Ca 125 measurement during follow-up

Research question	
Population	Patients with ovarian cancer in complete remission after first-line treatment
Intervention	Follow-up including routine Ca 125 measurement (with start of treatment if patient is still asymptomatic)
Comparator	Follow-up without routine Ca 125 measurement
Outcomes	Overall survival (6.1) Progression-free survival (5.9) Quality of life (4.6)



3. SEARCH STRATEGIES

3.1. Pre-operative assessment pelvic mass

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	15-06-2015	
Search Strategy	<ol style="list-style-type: none">1 exp Ovarian Neoplasms/2 (ovar* adj5 (cancer* or tumor* or tumour* or adenocarcinom* or carcinosarcom* or cystadenocarcinom* or carcinom* or malignan* or neoplas* or carcinogen* or teratoma* or metasta* or mass or masses)).mp.3 1 or 24 (risk adj3 malign* adj index).mp.5 rmi.mp.6 4 or 57 3 and 68 exp CA-125 Antigen/9 CA-125.mp.10 ultrasonography/11 ultraso*.mp.12 exp Menopause/13 menopaus*.mp.14 8 or 915 10 or 1116 12 or 1317 14 and 15 and 1618 6 or 1719 3 and 1820 case reports.pt.21 19 not 20	



Database	Ovid: Embase Classic+Embase 1947 to 2015 June 15
Date	15-06-2015
Search Strategy	<ol style="list-style-type: none">1 exp ovary tumor/2 (ovar* adj5 (cancer* or tumor* or tumour* or adenocarcinom* or carcinosarcom* or cystadenocarcinom* or carcinom* or malignan* or neoplas* or carcinogen* or teratoma* or metasta* or mass or masses)).mp.3 1 or 24 (risk adj3 malign* adj index).mp.5 rmi.mp.6 4 or 57 exp CA 125 antigen/8 ca-125.mp.9 exp echography/10 ultraso*.mp.11 exp menopause/12 menopaus*.mp.13 7 or 814 9 or 1015 11 or 1216 13 and 14 and 1517 6 or 1618 3 and 1719 case report/20 limit 18 to (conference abstract or conference paper or conference proceeding or "conference review")21 19 or 2022 18 not 21



Database	Cochrane library (Wiley)
Date	15-06-2015
Search Strategy	<div><div>#1</div><div>[mh ^"Ovarian Neoplasms"]</div><div>#2</div><div>(ovar* near/5 (cancer* or tumor* or tumour* or adenocarcinom* or carcinosarcom* or cystadenocarcinom* or carcinom* or malignan* or neoplas* or carcinogen* or teratoma* or metasta* or mass or masses)):ti,ab,kw</div><div>#3</div><div>#1 or #2</div><div>#4</div><div>(risk near/3 malign* near index):ti,ab,kw</div><div>#5</div><div>rmi:ti,ab,kw</div><div>#6</div><div>#4 or #5</div><div>#7</div><div>[mh ^"CA-125 Antigen"]</div><div>#8</div><div>ca-125:ti,ab,kw</div><div>#9</div><div>[mh ultrasonography]</div><div>#10</div><div>ultraso*:ti,ab,kw</div><div>#11</div><div>[mh Menopause]</div><div>#12</div><div>menopaus*:ti,ab,kw</div><div>#13</div><div>(#7 or #8) and (#9 or #10) and (#11 or #12)</div><div>#14</div><div>#13 or #6</div><div>#15</div><div>#14 and #3</div></div>



3.2. Intra-operative frozen section

3.2.1. Systematic reviews

Database	OvidSP Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	28-04-2015	
Search Strategy	1	exp Ovarian Neoplasms/
	2	(ovar* adj5 (cancer* or neoplasm* or carcinoma* or cystadenocarcinoma* or tumo?*r*)).ti,ab,kw.
	3	1 or 2
	4	exp Frozen Sections/
	5	(FS or FSA or IFS or IFSA).ti,ab,kw.
	6	((intraoperative or intra-operative) adj5 (consultation* or microscopy or immunohistochemistry or histolog* or diagnos* or patholog*)).ti,ab,kw.
	7	(cryosection* or cryogenic*).ti,ab,kw.
	8	((frozen or fresh or quick) adj5 (section* or tissue* or specimen*)).ti,ab,kw.
	9	4 or 5 or 6 or 7 or 8
	10	3 and 9
	11	animals/ not humans/
	12	10 not 11
	13	(MEDLINE or systematic review or (literature adj2 review)).tw. or (search* adj12 (literature or database?)).ti,ab. or intervention\$.ti.
	14	12 and 13
Note	SR filter based on healthcanada.ca article (PMID: 22512835)	

Database	OvidSP Embase Classic+Embase 1947 to 2015 April 27	
Date	28-04-2015	
Search Strategy	1	exp ovary tumor/
	2	(ovar* adj5 (cancer* or neoplasm* or carcinoma* or cystadenocarcinoma* or tumo?*r*)).ti,ab,kw.
	3	1 or 2
	4	frozen section/
	5	(FS or FSA or IFS or IFSA).ti,ab,kw.



- | | |
|----|--|
| 6 | ((intraoperative or intra-operative) adj5 (consultation* or microscopy or immunohistochemistry or histolog* or diagnos* or patholog*)).ti,ab,kw. |
| 7 | (cryosection* or cryogenic*).ti,ab,kw. |
| 8 | ((frozen or fresh or cryostat* or quick) adj5 (section* or tissue* or specimen*)).ti,ab,kw. |
| 9 | 4 or 5 or 6 or 7 or 8 |
| 10 | 3 and 9 |
| 11 | (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) |
| 12 | 10 not 11 |
| 13 | MEDLINE.tw. or exp systematic review/ or systematic review.tw. or (literature adj2 review).tw. or meta-analysis/ or (search* adj12 (literature or database?)).ti,ab. |
| 14 | 12 and 13 |
| 15 | limit 14 to (conference abstract or conference paper or conference proceeding) |
| 16 | 14 not 15 |

Note

SR filter based on healthcanada.ca article (PMID: 22512835)

Database

Thecochranelibrary.com

*Cochrane database of systematic reviews

*Database of Abstracts of Reviews of Effects

Date

28-04-2015

Search Strategy

- | | |
|----|---|
| #1 | MeSH descriptor: [Ovarian Neoplasms] explode all trees |
| #2 | (ovar* near/5 (cancer* or neoplasm* or carcinoma* or cystadenocarcinoma* or tumo?r*)):ti,ab,kw |
| #3 | #1 or #2 |
| #4 | MeSH descriptor: [Frozen Sections] explode all trees |
| #5 | (FS or FSA or IFS or IFSA):ti,ab,kw |
| #6 | ((intraoperative or intra-operative) near/5 (consultation* or microscopy or immunohistochemistry or histolog* or diagnos* or patholog*)):ti,ab,kw |
| #7 | (cryosection* or cryogenic*):ti,ab,kw |
| #8 | ((frozen or fresh or cryostat* or quick) near/5 (section* or tissue* or specimen*)):ti,ab,kw |
| #9 | #4 or #5 or #6 or #7 or #8 |



#10 #3 and #9

Note*3.2.2. Randomized controlled trials*

Database	OvidSP Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	29-04-2015	
Search Strategy	1	exp Ovarian Neoplasms/
	2	(ovar* adj5 (cancer* or neoplasm* or carcinoma* or cystadenocarcinoma* or tumo?*r*)).ti,ab,kw.
	3	1 or 2
	4	exp Frozen Sections/
	5	(FS or FSA or IFS or IFSA).ti,ab,kw.
	6	((intraoperative or intra-operative) adj5 (consultation* or microscopy or immunohistochemistry or histolog* or diagnos* or patholog*)).ti,ab,kw.
	7	(cryosection* or cryogenic*).ti,ab,kw.
	8	((frozen or fresh or quick) adj5 (section* or tissue* or specimen*)).ti,ab,kw.
	9	4 or 5 or 6 or 7 or 8
	10	3 and 9
	11	animals/ not humans/
	12	10 not 11
	13	(randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or trial.ab. or groups.ab.
	14	12 and 13
Note	Adapted Cochrane highly sensitive, specific RCT filter	

Database	OvidSP Embase Classic+Embase 1947 to 2015 April 28	
Date	29-04-2015	
Search Strategy	1	exp ovary tumor/
	2	(ovar* adj5 (cancer* or neoplasm* or carcinoma* or cystadenocarcinoma* or tumo?*r*)).ti,ab,kw.
	3	1 or 2
	4	frozen section/



5	(FS or FSA or IFS or IFSA).ti,ab,kw.
6	((intraoperative or intra-operative) adj5 (consultation* or microscopy or immunohistochemistry or histolog* or diagnos* or patholog*)).ti,ab,kw.
7	(cryosection* or cryogenic*).ti,ab,kw.
8	((frozen or fresh or cryostat* or quick) adj5 (section* or tissue* or specimen*)).ti,ab,kw.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
12	10 not 11
13	limit 12 to (conference abstract or conference paper or conference proceeding or "conference review")
14	12 not 13
15	crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ or crossover\$.ti,ab,ot. or cross over\$.ti,ab,ot. or placebo\$.ti,ab,ot. or (doubl\$ adj blind\$).ti,ab,ot. or allocat\$.ti,ab,ot. or random\$.ti,ab,ab. or trial\$.ti.
16	14 and 15

Note

Cochrane filter for RCTs

Database	Cochrane central registry of studies (via CRSO gateway, crso.cochrane.org)	
Date	29-04-2015	
Search Strategy	#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
	#2	(ovar* near/5 (cancer* or neoplasm* or carcinoma* or cystadenocarcinoma* or tumo?r*)):ti,ab,kw
	#3	#1 or #2
	#4	MeSH descriptor: [Frozen Sections] explode all trees
	#5	(FS or FSA or IFS or IFSA):ti,ab,kw
	#6	((intraoperative or intra-operative) near/5 (consultation* or microscopy or immunohistochemistry or histolog* or diagnos* or patholog*)).ti,ab,kw
	#7	(cryosection* or cryogenic*):ti,ab,kw
	#8	((frozen or fresh or cryostat* or quick) near/5 (section* or tissue* or specimen*)):ti,ab,kw
	#9	#4 or #5 or #6 or #7 or #8
	#10	#3 and #9
Note		



3.2.3. Diagnostic test accuracy studies

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	4-5-2015	
Search Strategy	1	exp Ovarian Neoplasms/
	2	(ovar* adj5 (cancer* or tumor* or tumour* or adenocarcinoma* or carcinosarcoma* or cystadenocarcinoma* or carcinoma* or malignan* or neoplas* or carcinogen* or teratoma* or metasta* or mass or masses)).tw,ot.
	3	(thecoma* or luteoma*).tw,ot.
	4	1 or 2 or 3
	5	Frozen Sections/
	6	(FS or FSA or IFS or IFSA).tw,ot.
	7	((frozen or quick) adj5 section*).tw,ot.
	8	((intraoperative or intra-operative) adj5 (consultation* or histolog* or diagnos* or patholog*)).tw,ot.
	9	(cryosection* or cryogenic*).tw,ot.
	10	((fresh or frozen) adj5 tissue*).tw,ot.
	11	5 or 6 or 7 or 8 or 9 or 10
	12	4 and 11
	13	exp animals/ not humans.sh.
	14	(randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or trial.ab. or groups.ab.
	15	(MEDLINE or systematic review or (literature adj2 review)).tw. or (search* adj12 (literature or database?)).ti,ab. or intervention\$.ti.
	16	13 or 14 or 15
	17	12 not 16
	18	limit 17 to yr="2009 -Current"
Note	See line 17: reviews and RCTs were subtracted	

Database	OvidSP Embase Classic+Embase 1947 to 2015 May 3	
Date	4-5-2015	
Search Strategy	1	exp Ovarian Neoplasms/



- 2 (ovar* adj5 (cancer* or tumor* or tumour* or adenocarcinoma* or carcinosarcoma* or cystadenocarcinoma* or carcinoma* or malignan* or neoplas* or carcinogen* or teratoma* or metasta* or mass or masses)).tw,ot.
- 3 (thecoma* or luteoma*).tw,ot.
- 4 1 or 2 or 3
- 5 Frozen Sections/
- 6 (FS or FSA or IFS or IFSA).tw,ot.
- 7 ((frozen or quick) adj5 section*).tw,ot.
- 8 ((intraoperative or intra-operative) adj5 (consultation* or histolog* or diagnos* or patholog*)).tw,ot.
- 9 (cryosection* or cryogenic*).tw,ot.
- 10 ((fresh or frozen) adj5 tissue*).tw,ot.
- 11 5 or 6 or 7 or 8 or 9 or 10
- 12 4 and 11
- 13 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
- 14 crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ or crossover\$.ti,ab,ot. or cross over\$.ti,ab,ot. or placebo\$.ti,ab,ot. or (doubl\$ adj blind\$).ti,ab,ot. or allocat\$.ti,ab,ot. or random\$.ti,ab,ab. or trial\$.ti.
- 15 MEDLINE.tw. or exp systematic review/ or systematic review.tw. or (literature adj2 review).tw. or meta-analysis/ or (search* adj12 (literature or database?)).ti,ab.
- 16 13 or 14 or 15
- 17 12 not 16
- 18 limit 17 to (conference abstract or conference paper or conference proceeding or "conference review")
- 19 17 not 18
- 20 limit 19 to yr="2009 -Current"

Note

See line 19: reviews and RCTs were subtracted



3.3. Lymphadenectomy

3.3.1. Systematic reviews

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date	15-06-2015
Search Strategy	<ol style="list-style-type: none">1 exp Ovarian Neoplasms/2 (ovar* adj5 (cancer* or neoplasm* or carcinom* or malignan* or tumor* or tumour*)).mp.3 1 or 24 exp Lymph Node Excision/5 (lymph adj5 node* adj5 (excis* or dissect* or surg*)).mp.6 lymphadenectomy.mp.7 4 or 5 or 68 3 and 79 case reports.pt.10 8 not 911 (MEDLINE or systematic review or (literature adj2 review)).tw. or (search* adj12 (literature or database?)).ti,ab. or intervention\$.ti.12 10 and 11
Note	SR filter health-evidence Canada (Lee E et al 2012 BMC medical research methodology)

Database	Ovid: Embase Classic+Embase 1947 to 2015 June 12
Date	15-06-2015
Search Strategy	<ol style="list-style-type: none">1 exp ovary tumor/2 (ovar* adj5 (cancer* or neoplasm* or carcinom* or malignan* or tumor* or tumour*)).mp.3 1 or 24 exp lymph node dissection/5 (lymph adj5 node* adj5 (excis* or dissect* or surg*)).mp.6 lymphadenectomy.mp.



- 7 4 or 5 or 6
- 8 3 and 7
- 9 MEDLINE.tw. or exp systematic review/ or systematic review.tw. or meta-analysis/ or (search* adj12 (literature or database?)).ti,ab.
- 10 8 and 9
- 11 limit 10 to (conference abstract or conference paper or conference proceeding or "conference review")
- 12 10 not 11

Note SR filter health-evidence Canada (Lee E et al 2012 BMC medical research methodology)

Database Cochrane library (Wiley)

Date 15-06-2015

Search Strategy

- #1 [mh ^"Ovarian Neoplasms"]
- #2 (ovar* near/5 (cancer* or neoplasm* or carcinom* or malignan* or tumor* or tumour*)):ti,ab,kw
- #3 #1 or #2
- #4 [mh ^" Lymph Node Excision"]
- #5 (lymph near/5 node* near/5 (excis* or dissect* or surg*)):ti,ab,kw
- #6 lymphadenectomy:ti,ab,kw
- #7 #4 or #5 or #6
- #8 #7 and #3

Note

3.3.2. Primary studies

Database Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Date 22-06-2015

Search Strategy

- 1 exp Ovarian Neoplasms/
- 2 (ovar* adj5 (cancer* or neoplasm* or carcinom* or malignan* or tumor* or tumour*)):mp.
- 3 1 or 2
- 4 exp Lymph Node Excision/



- 5 (lymph adj5 node* adj5 (excis* or dissect* or surg*)).mp.
- 6 lymphadenectomy.mp.
- 7 4 or 5 or 6
- 8 3 and 7
- 9 case reports.pt.
- 10 8 not 9

Note

Database	Ovid: Embase Classic+Embase 1947 to 2015 June 18
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Date	22-06-2015
-------------	------------

- | | |
|------------------------|---|
| Search Strategy | <ol style="list-style-type: none">1 exp ovary tumor/2 (ovar* adj5 (cancer* or neoplasm* or carcinom* or malignan* or tumor* or tumour*)).mp.3 1 or 24 exp lymph node dissection/5 (lymph adj5 node* adj5 (excis* or dissect* or surg*)).mp.6 lymphadenectomy.mp.7 4 or 5 or 68 3 and 79 case report/10 limit 8 to (conference abstract or conference paper or conference proceeding or "conference review")11 9 or 1012 8 not 11 |
|------------------------|---|

Note

Date	Cochrane library (Wiley)
-------------	---------------------------------

Database	22-06-2015
-----------------	------------



Search Strategy	ID	Search
	#1	[mh ^"Ovarian Neoplasms"]
	#2	(ovar* near/5 (cancer* or neoplasm* or carcinom* or malignan* or tumor* or tumour*)):ti,ab,kw
	#3	#1 or #2
	#4	[mh ^"Lymph Node Excision"]
	#5	(lymph near/5 node* near/5 (excis* or dissect* or surg*)):ti,ab,kw
	#6	lymphadenectomy:ti,ab,kw
	#7	#4 or #5 or #6
	#8	#3 and #7

Note

3.4. Adjuvant chemotherapy

3.4.1. RCTs and non-randomized studies

3.4.1.1. Borderline ovarian tumours

Database	Ovid MEDLINE(R) 2009 to Present
Date	24-03-2015
Search Strategy	<ol style="list-style-type: none">1. exp Ovarian Neoplasms/2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)):mp.3. 1 or 24. (atypical adj proliferative).mp.5. borderline.mp.6. micropapillary.mp.7. (low adj malignan*).mp.8. (semi adj malignan*).mp.9. 4 or 5 or 6 or 7 or 810. 3 and 911. (ovar* adj5 cystadeno*).mp.12. 10 or 1113. "randomized controlled trial".pt.



14. "controlled clinical trial".pt.
15. randomized.ab.
16. placebo.ab.
17. "drug therapy".fs.
18. "surgery".fs.
19. "therapy".fs.
20. "radiotherapy".fs.
21. randomly.ab.
22. trial.ab.
23. groups.ab.
24. exp Cohort Studies/
25. cohort*.mp.
26. (case adj series).mp.
27. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 12 and 27
29. Animals/
30. Humans/
31. 29 not (29 and 30)
32. 28 not 31

Note

Search for RCTs regarding RQ5a (Faluyi 2010: Interventions for the treatment of borderline ovarian tumours)

Database

Ovid Embase 2009 to current

Date

24-03-2015

Search Strategy

1. Ovary Tumor/
2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. (atypical adj proliferative).mp.
5. borderline.mp.
6. micropapillary.mp.
7. (low adj malignan*).mp.]



8. (semi adj malignan*).mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9
11. (ovar* adj5 cystadeno*).mp.
12. 10 or 11
13. exp Controlled Clinical Trial/
14. randomized.ab.
15. placebo.ab.
16. dt.fs.
17. su.fs.
18. th.fs.
19. rt.fs.
20. randomly.ab.
21. trial.ab.
22. groups.ab.
23. exp Cohort Analysis/
24. cohort*.mp.
25. (case adj series).mp.
26. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 12 and 26
28. exp Animal/
29. Human/
30. 28 not (28 and 29)
31. 27 not 30

Note	Search for RCTs regarding RQ5a (Faluyi 2010: Interventions for the treatment of borderline ovarian tumours)
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Database	Cochrane Central (Issue 2, 2015)
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Date	24-03-2015
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Search Strategy	1. MeSH descriptor Ovarian Neoplasms explode all trees 2. ovar* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)
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3. (#1 OR #2)
4. atypical adj proliferative
5. borderline
6. micropapillary
7. low adj malignan*
8. semi adj malignan*
9. (#4 OR #5 OR #6 OR #7 OR #8)
10. (#3 AND #9)
11. ovar* near/5 cystadeno*
12. (#10 OR #11)

Note Search for RCTs regarding RQ5a (Faluyi 2010: Interventions for the treatment of borderline ovarian tumours)

3.4.1.2. Micro-invasive disease

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	08-04-2015	
Search Strategy	1	exp Ovarian Neoplasms/
	2	(ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).ti,ab,kw.
	3	or/1-2 [ovarian cancer]
	4	borderline.ti,ab,kw.
	5	(low adj malignan*).ti,ab,kw.
	6	Imp.ti,ab,kw.
	7	or/4-6 [borderline]
	8	microinvasi*.ti,ab,kw.
	9	micro-invasi*.ti,ab,kw.
	10	or/8-9 [microinvasive]
	11	(ovar* adj5 cystadeno*).ti,ab,kw.
	12	7 or 10
	13	3 and 12
	14	11 or 13
	15	exp Chemotherapy, Adjuvant/ or exp Chemoradiotherapy, Adjuvant/ or exp Radiotherapy, Adjuvant/
	16	adjuvant.ti,ab,kw.



	17	15 or 16
	18	14 and 17
Note	Search for RCTs and non-randomized studies regarding RQ5b	

Database	Embase Classic+Embase 1947 to 2015 April 07	
Date	08-04-2015 Ovid	
Search Strategy	1	Ovary Tumor/
	2	(ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).ti,ab,kw.
	3	or/1-2 [ovarian cancer]
	4	borderline.ti,ab,kw.
	5	(low adj malignan*).ti,ab,kw.
	6	Imp.ti,ab,kw.
	7	or/4-6 [borderline]
	8	microinvasi*.ti,ab,kw.
	9	micro-invasi*.ti,ab,kw.
	10	or/8-9 [microinvasive]
	11	(ovar* adj5 cystadeno*).ti,ab,kw.
	12	7 or 10
	13	3 and 12
	14	11 or 13
	15	exp adjuvant therapy/ or exp adjuvant/ or exp adjuvant chemotherapy/ or exp adjuvant chemoradiotherapy/ or exp cancer adjuvant therapy/
	16	adjuvant.ti,ab,kw.
	17	15 or 16
	18	14 and 17
	19	limit 18 to (conference abstract or conference paper or conference proceeding or "conference review")
	20	18 not 19
Note	Search for RCTs and non-randomized studies regarding RQ5b	



Database	PubMed Central
Date	08-04-2015
Search Strategy	(microinvasive[TW] OR micro-invasive[tw] OR microinvasion[TW] OR micro-invasion[tw]) AND (ovarian cancer[TI] OR ovarian neoplasm*[TI] OR ovarian cancer[AB] OR ovarian neoplasm*[AB] OR "ovarian neoplasms"[MeSH Terms]) AND ("Chemoradiotherapy, Adjuvant"[mesh] OR "Radiotherapy, Adjuvant"[mesh] OR "Chemoradiotherapy, Adjuvant"[mesh] OR adjuvant[TW])
Note	Search for RCTs and non-randomized studies regarding RQ5b

3.4.1.3. Invasive early stage epithelial ovarian cancer

Database	Ovid MEDLINE(R) 2011 to Present
Date	24-03-2015
Search Strategy	<ol style="list-style-type: none">1. exp Ovarian Neoplasms/2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*)).mp.3. 1 or 24. drug therapy.fs.5. exp Antineoplastic Agents/6. Antineoplastic Combined Chemotherapy Protocols/7. chemotherap*.mp.8. 4 or 5 or 6 or 79. surgery.fs.10. exp Surgical Procedures, Operative/11. (surg* or procedure* or intervention*).mp.12. 9 or 10 or 1113. 8 and 1214. Chemotherapy, Adjuvant/15. (chemotherap* and adjuvant).mp.16. 14 or 1517. 13 or 1618. 3 and 1719. randomized controlled trial.pt.



- 20. controlled clinical trial.pt.
- 21. randomized.ab.
- 22. placebo.ab.
- 23. clinical trials as topic.sh.
- 24. randomly.ab.
- 25. trial.ti.
- 26. 19 or 20 or 21 or 22 or 23 or 24 or 25
- 27. 18 and 26

Note	Search for RCTs regarding RQ5c (Winter-Roach 2012: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer)
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Database	Ovid Embase 2011 to current
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Date	24-03-2015
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Search Strategy	<ul style="list-style-type: none">1 exp ovary tumor/2 (ovar* adj5 (cancer* or tumor* or tumour* or malignan* or carcinoma* or neoplasm*)).mp.3 1 or 24 exp chemotherapy/5 exp antineoplastic agent/6 chemotherap*.mp.7 4 or 5 or 68 exp gynecologic surgery/9 (surgery or surgical* or procedure* or intervention*).mp.10 8 or 911 7 and 1012 adjuvant chemotherapy/13 (adjuvant adj5 chemotherap*).mp.14 12 or 1315 11 or 1416 3 and 1517 crossover procedure/
------------------------	---



18 randomized controlled trial/
19 single blind procedure/
20 random*.mp.
21 factorial*.mp.
22 (crossover* or cross over* or cross-over).mp.
23 placebo*.mp.
24 (doubl* adj blind*).mp.
25 (singl* adj blind*).mp.
26 assign*.mp.
27 allocat*.mp.
28 volunteer*.mp.
29 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 16 and 29

Note

Search for RCTs regarding RQ5c (Winter-Roach 2012: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer)

Database

Cochrane Central (Issue 2, 2015)

Date

24-03-2015

Search Strategy

1 MeSH descriptor Ovarian Neoplasms explode all trees
2 ovar* near/5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*)
3 (#1 OR #2)
4 Any MeSH descriptor with qualifier: DT
5 MeSH descriptor Antineoplastic Agents explode all trees
6 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols, this term only
7 chemotherap*
8 (#4 OR #5 OR #6 OR #7)
9 Any MeSH descriptor with qualifier: SU
10 MeSH descriptor Surgical Procedures, Operative explode all trees
11 surg* or procedure* or intervention*
12 (#9 OR #10 OR #11)



13 (#8 AND #12)
14 MeSH descriptor Chemotherapy, Adjuvant explode all trees
15 chemotherap* and adjuvant
16 (#14 OR #15)
17 (#13 OR #16)
18 (#3 AND #17)

Note Search for RCTs regarding (Winter-Roach 2012: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer)

3.5. Laparoscopic surgery

3.5.1. Systematic reviews

Database	Medline OvidSP
Date	2015-03-09
Search strategy	
1	exp Ovarian Neoplasms/ 65326
2	(ovar* adj5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcin* or adenocarcin* or metasta*)).tw. 68272
3	1 or 2 85995
4	exp Laparoscopy/ 71161
5	laparoscop*.ab,ti. 86822
6	peritoneoscop*.ab,ti. 720
7	celioscop*.ab,ti. 548
8	Laparotomy/ 15757
9	(endoscop* adj5 abdom*).ab,ti. 1336
10	laparotom*.ab,ti. 39237
11	(abdom* adj5 (surg* or incision)).ab,ti. 25235
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 156391
13	3 and 12 5036



14	limit 13 to systematic reviews	68
15	randomized controlled trial.pt.	387168
16	controlled clinical trial.pt.	88869
17	randomized.ti,ab.	333894
18	placebo.ti,ab.	163360
19	clinical trials as topic/	171370
20	randomly.ti,ab.	226003
21	trial?.ti.	182508
22	15 or 16 or 17 or 18 or 19 or 20 or 21	963148
23	exp animal/ not humans/	4000190
24	22 not 23	888683
25	13 and 24	299
26	limit 25 to yr="2006 -Current"	86

Notes

Database	Embase
Date	2015-03-09
Search strategy	
1	'ovary tumor'/exp 105023
2	(ovar* NEAR/5 (cancer* OR tumor* OR tumour* OR neoplas* OR carcin* OR adenocarcin* OR malignan* OR metastas*)) :ab,ti 88199
3	#1 OR #2 121355
4	'laparoscopy'/exp 106372
5	'laparotomy'/exp 56282



6	laparotom*:ab,ti	50815
7	laparoscop*:ab,ti	128212
8	peritoneoscop*:ab,ti	966
9	celioscop*:ab,ti	548
10	(endoscop* NEAR/5 abdom*):ab,ti	2113
11	(abdom* NEAR/5 (surg* OR incision)):ab,ti	33841
12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	239712
13	#3 AND #12	8657
14	#13 NOT [medline]/lim	2798
15	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	193662
16	#14 AND #15	33
17	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1170050
18	#14 AND #17	109
19	#14 AND #17 AND [2006-2015]/py	83

Notes

Database	Cochrane Database of Systematic Reviews		
Date	06/03/15 14:57:39.376		
Search strategy			
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees		1411
#2	ovar* near/5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcino* or adenocarcino* or metasta*):ab,ti		3214
#3	#1 or #2		3390
#4	MeSH descriptor: [Laparoscopy] explode all trees		4937



#5	MeSH descriptor: [Laparotomy] explode all trees	719
#6	laparoscop*:ab,ti	8419
#7	laparotom*:ab,ti	1404
#8	celioscop*:ab,ti	10
#9	peritoneoscop*:ab,ti	14
#10	(endoscop* near/5 abdom*):ab,ti	74
#11	(abdom* near/5 (surg* or incision)):ab,ti	4305
#12	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	13655
#13	#3 and #12	196
#14	#3 and #12 Publication Year from 2006 to 2015	64

Notes*3.5.2. Primary studies*

Database	Medlina via Ovid
Date	12/10/2015
	1 exp Ovarian Neoplasms/ (68760)
	2 (ovar* adj5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcin* or adenocarcin* or metastas*)).tw. (72299)
	3 1 or 2 (90701)
	4 exp Laparoscopy/ (75144)
	5 laparoscop*.ab,ti. (91564)
	6 peritoneoscop*.ab,ti. (730)
	7 celioscop*.ab,ti. (553)
	8 Laparotomy/ (16313)
	9 (endoscop* adj5 abdom*).ab,ti. (1416)
	10 laparotom*.ab,ti. (40849)
	11 (abdom* adj5 (surg* or incision)).ab,ti. (26595)



- 12 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (164278)
- 13 3 and 12 (5230)
- 14 exp animal/ not humans/ (4130605)
- 15 13 not 14 (5148)
- 16 limit 15 to yr="2014 -Current" (343)
- 17 remove duplicates from 16 (336)

Notes

Database	Embase via embase.com		
Date	12/10/2015		
No.	Query	Results	
#31	#17 AND #30	73	
#30	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	2820026	
#29	'clinical trials'/exp	164445	
#28	'observational studies'/exp	79758	
#27	'case control':ab,ti	107200	
#26	'case control studies'/exp	101416	
#25	observational:ab,ti	136689	
#24	retrospective:ab,ti	482170	
#23	prospective:ab,ti	547746	
#22	longitudinal:ab,ti	201417	
#21	placebo:ab,ti	224091	
#20	random*:ab,ti	1018310	
#19	trial:ab,ti	548333	
#18	cohort:ab,ti	460409	
#17	#15 NOT #16	397	
#16	#13 NOT [medline]/lim AND [2014-2015]/py AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim)	278	
#15	#13 NOT [medline]/lim AND [2014-2015]/py	675	
#14	#13 NOT [medline]/lim	2979	



#13 #3 AND #12	9048
#12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	254203
#11 (abdom* NEAR/5 (surg* OR incision)):ab,ti	35769
#10 (endoscop* NEAR/5 abdom*):ab,ti	2240
#9 celioscop*:ab,ti	554
#8 peritoneoscop*:ab,ti	987
#7 laparoscop*:ab,ti	137734
#6 laparotom*:ab,ti	52873
#5 'laparotomy'/exp	59121
#4 'laparoscopy'/exp	112826
#3 #1 OR #2	127662
#2 (ovar* NEAR/5 (cancer* OR tumor* OR tumour* OR neoplas* OR carcin* OR adenocarcin* OR malignan* OR metasta*)):ab,ti	93171
#1 'ovary tumor'/exp	109809

Notes

Database	Cochrane		
Date	12/10/2015		
#1	[mh "ovarian neoplasms"]	1433	
#2	ovar* near/5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcino* or adenocarcino* or metasta*):ab,ti		3417
#3	#1 or #2	3594	
#4	[mh laparoscopy]	5052	
#5	[mh laparotomy]	725	
#6	laparoscop*:ab,ti	9249	
#7	laparotom*:ab,ti	1482	
#8	celioscop*:ab,ti	10	
#9	peritoneoscop*:ab,ti	15	
#10	(endoscop* near/5 abdom*):ab,ti	84	
#11	(abdom* near/5 (surg* or incision)):ab,ti	4655	
#12	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	14818	



#13	#3 and #12	203
#14	#3 and #12 Publication Year from 2014 to 2015 13	

Notes

3.6. Laparoscopy, PET-CT and MRI to predict end result of cytoreductive surgery

3.6.1. Systematic reviews

Database	OvidSP Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	22-01-2015	
Search Strategy	1	exp Ovarian Neoplasms/
	2	(ovar* adj5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or tumo?r)).ti,ab,kw.
	3	1 or 2
	4	exp Magnetic Resonance Imaging/
	5	(magn* adj3 imag*).ti,ab,kw.
	6	mri.ti,ab,kw.
	7	exp Positron-Emission Tomography/
	8	(pet adj3 scan*).ti,ab,kw.
	9	(positr* adj4 tomogr*).ti,ab,kw.
	10	exp Laparoscopy/
	11	laparoscop*.ti,ab,kw.
	12	or/4-11
	13	3 and 12
	14	(MEDLINE or systematic review).tw. or (search* adj12 (literature or database?)).ti,ab. or intervention\$.ti.
	15	13 and 14
Note	SR filter based on healthcanada.ca article (PMID: 22512835)	

Database	OvidSP Embase Classic+Embase 1947 to 2015 January 20	
Date	22-01-2015	
Search Strategy	1	exp ovary cancer/



- | | |
|----|--|
| 2 | (ovar* adj5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or tumo?r)).ti,ab,kw. |
| 3 | 1 or 2 |
| 4 | exp nuclear magnetic resonance imaging/ |
| 5 | (magn* adj3 imag*).ti,ab,kw. |
| 6 | mri.ti,ab,kw. |
| 7 | exp positron emission tomography/ |
| 8 | (pet adj3 scan*).ti,ab,kw. |
| 9 | (positr* adj4 tomogr*).ti,ab,kw. |
| 10 | exp laparoscopy/ |
| 11 | laparoscop*.ti,ab,kw. |
| 12 | or/4-11 |
| 13 | MEDLINE.tw. or exp systematic review/ or systematic review.tw. or meta-analysis/ or (search* adj12 (literature or database?)).ti,ab. |
| 14 | 3 and 12 and 13 |

Note

SR filter based on healthcanada.ca article (PMID: 22512835)

Database

Thecochranelibrary.com
*Cochrane database of systematic reviews
*Database of Abstracts of Reviews of Effects

Date

22-01-2015

Search Strategy

- | | |
|----|---|
| #1 | MeSH descriptor: [Ovarian Neoplasms] explode all trees |
| #2 | (ovar* next/5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or tumo?r)).ti,ab,kw |
| #3 | #1 or #2 |
| #4 | [mh ^"Magnetic Resonance Imaging"] |
| #5 | (magn* next/3 imag*).ti,ab,kw |
| #6 | mri:ti,ab,kw |
| #7 | [mh ^"Positron-Emission Tomography"] |
| #8 | (pet near/3 scan*).ti,ab,kw |
| #9 | (positr* near/4 tomogr*).ti,ab,kw |



- | | |
|-----|--|
| #10 | [mh ^Laparoscopy] |
| #11 | laparoscop*.ti,ab,kw |
| #12 | #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 |
| #13 | #3 and #12 |

3.6.2. RCTs

Database	OvidSP Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	16-02-2015	
Search Strategy	1	exp Ovarian Neoplasms/
	2	(ovar* adj5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or malign* or tumo?r)).ti,ab,kw.
	3	1 or 2
	4	exp Magnetic Resonance Imaging/
	5	MRi.ti,ab,kw.
	6	(magn* adj3 imag*).ti,ab,kw.
	7	(Diffusion adj3 Imaging).ti,ab,kw.
	8	Diffusion-weighted.ti,ab,kw.
	9	or/4-8
	10	exp Positron-Emission Tomography/
	11	(pet adj3 scan*).ti,ab,kw.
	12	(positr* adj4 tomogr*).ti,ab,kw.
	13	("Positron emission tomography" adj3 "computed tomography").ti,ab,kw.
	14	(pet-ct or "pet/ct" or fdg-pet).ti,ab,kw.
	15	or/10-14
	16	9 or 15
	17	3 and 16
	18	exp Ovarian Neoplasms/ri
	19	17 or 18
	20	(randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or (random* or placebo).ti,ab,kw,hw. or trial.ti.
	21	19 and 20
Note	Adapted Cochrane highly sensitive, specific RCT filter	



Database		OvidSP Embase Classic+Embase 1947 to 2015 February 13
Date		16-02-2015
Search Strategy		<ol style="list-style-type: none">1 exp *ovary cancer/2 (ovar* adj5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or malign* or tumo?r)).ti,ab,kw.3 1 or 24 exp nuclear magnetic resonance imaging/5 MRi.ti,ab,kw.6 (magn* adj3 imag*).ti,ab,kw.7 (Diffusion adj3 Imaging).ti,ab,kw.8 Diffusion-weighted.ti,ab,kw.9 4 or 5 or 6 or 7 or 810 exp positron emission tomography/11 (pet adj3 scan*).ti,ab,kw.12 (positr* adj4 tomogr*).ti,ab,kw.13 ("Positron emission tomography" adj3 "computed tomography").ti,ab,kw.14 (pet-ct or "pet/ct" or fdg-pet).ti,ab,kw.15 or/10-1416 9 or 1517 3 and 1618 crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ or crossover\$.ti,ab,ot. or cross over\$.ti,ab,ot. or placebo\$.ti,ab,ot. or (doubl\$ adj blind\$).ti,ab,ot. or allocat\$.ti,ab,ot. or random\$.ti,ab,ab. or trial\$.ti.19 17 and 18
Note		Cochrane filter for RCTs

Database		Cochrane central registry of studies (via CRSO gateway, crso.cochrane.org)
Date		16-02-2015
Search Strategy		<ol style="list-style-type: none">#1 Ovarian Neoplasms:MH#2 ovary cancer:EH#3 (ovar* adj5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or malign* or tumo?r)).ti,ab,kw#4 #1 OR #2 OR #3



- #5 Magnetic Resonance Imaging:MH
- #6 nuclear magnetic resonance imaging:EH
- #7 MRi:ti,ab,kw
- #8 (magn* adj3 imag*):ti,ab,kw
- #9 (Diffusion adj3 Imaging):ti,ab,kw
- #10 Diffusion-weighted:ti,ab,kw
- #11 #5 OR #6 OR #7 OR #8 OR #9 OR #10
- #12 positron emission tomography:EH
- #13 Positron-Emission Tomography:MH
- #14 (pet adj3 scan*):ti,ab,kw
- #15 (positr* adj4 tomogr*):ti,ab,kw
- #16 ("Positron emission tomography" adj3 "computed tomography"):ti,ab,kw
- #17 (pet-ct or "pet/ct" or fdg-pet):ti,ab,kw
- #18 #12 OR #13 OR #14 OR #15 OR #16 OR #17
- #19 #11 OR #18
- #20 #4 AND #19
- #21 MESH DESCRIPTOR Ovarian Neoplasms EXPLODE ALL TREES WITH QUALIFIERS RI
- #22 #20 OR #21

3.6.3. Diagnostic accuracy studies

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date	7-2-2015	
Search Strategy	1	exp Ovarian Neoplasms/
	2	(ovar* adj5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or malign* or tumo?r)).ti,ab,kw.
	3	1 or 2
	4	exp Magnetic Resonance Imaging/
	5	MRi.ti,ab,kw.
	6	(magn* adj3 imag*).ti,ab,kw.
	7	(Diffusion adj3 Imaging).ti,ab,kw.
	8	Diffusion-weighted.ti,ab,kw.
	9	or/4-8



- | | |
|----|--|
| 10 | exp Positron-Emission Tomography/ |
| 11 | (pet adj3 scan*).ti,ab,kw. |
| 12 | (positr* adj4 tomogr*).ti,ab,kw. |
| 13 | ("Positron emission tomography" adj3 "computed tomography").ti,ab,kw. |
| 14 | (pet-ct or "pet/ct" or fdg-pet).ti,ab,kw. |
| 15 | or/10-14 |
| 16 | 9 or 15 |
| 17 | 3 and 16 |
| 18 | exp Ovarian Neoplasms/ri |
| 19 | 17 or 18 |
| 20 | (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or (random* or placebo).ti,ab,kw,hw. or trial.ti. |
| 21 | case reports.pt. |
| 22 | 20 or 21 |
| 23 | 19 not 22 |

Note	See line 23: case reports and RCTs were subtracted
-------------	--

Database	OvidSP Embase Classic+Embase 1947 to 2015 February 17
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Date	7-2-2015
-------------	----------

Search Strategy	1	exp *ovary cancer/
	2	(ovar* adj5 (cancer or neoplasm or carcinoma or cystadenocarcinoma or malign* or tumo?r)).ti,ab,kw.
	3	1 or 2
	4	exp nuclear magnetic resonance imaging/
	5	MRi.ti,ab,kw.
	6	(magn* adj3 imag*).ti,ab,kw.
	7	(Diffusion adj3 Imaging).ti,ab,kw.
	8	Diffusion-weighted.ti,ab,kw.
	9	4 or 5 or 6 or 7 or 8
	10	exp positron emission tomography/
	11	(pet adj3 scan*).ti,ab,kw.



- | | |
|----|---|
| 12 | (positr* adj4 tomogr*).ti,ab,kw. |
| 13 | ("Positron emission tomography" adj3 "computed tomography").ti,ab,kw. |
| 14 | (pet-ct or "pet/ct" or fdg-pet).ti,ab,kw. |
| 15 | or/10-14 |
| 16 | 9 or 15 |
| 17 | 3 and 16 |
| 18 | crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ or crossover\$.ti,ab,ot. or cross over\$.ti,ab,ot. or placebo\$.ti,ab,ot. or (doubl\$ adj blind\$).ti,ab,ot. or allocat\$.ti,ab,ot. or random\$.ti,ab,ab. or trial\$.ti. |
| 19 | case report/ |
| 20 | 18 or 19 |
| 21 | 17 not 20 |

Note	See line 21: case reports and RCTs were subtracted
-------------	--

3.7. Aim of cytoreductive surgery: no macroscopic disease?

3.7.1. RCTs and comparative observational studies – update Elattar 2011

Database	Medline OVID (including PreMEDLINE)
Date	16-01-2015
Search Strategy	<ol style="list-style-type: none">1. exp Ovarian Neoplasms/2. (ovar* adj5 cancer*).mp.3. (ovar* adj5 neoplas*).mp.4. (ovar* adj5 carcinom*).mp.5. (ovar* adj5 malignan*).mp.6. (ovar* adj5 tumor*).mp.7. (ovar* adj5 tumour*).mp.8. 1 or 2 or 3 or 4 or 5 or 6 or 79. exp Surgical Procedures, Operative/10. surg*.mp.11. "surgery".fs.12. 9 or 10 or 1113. debulk*.mp.



14. cytoeduc*.mp.
15. 13 or 14
16. 8 and 12 and 15
17. "randomized controlled trial".pt.
18. "controlled clinical trial".pt.
19. random*.mp.
20. trial*.mp.
21. group*.mp.
22. exp Cohort Studies/
23. cohort*.mp.
24. series.mp.
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 16 and 25
27. Animals/
28. Humans/
29. 27 not (27 and 28)
30. 26 not 29

Note

Search performed by Jane Hayes, Information Manager, Cochrane Gynaecologic, Neuro-oncology and Orphan Cancer Group (update of Elattar 2011 up to Jan week 2, 2015)

Database**Embase OVID****Date**

16-01-2015

Search Strategy

1. exp Ovary Tumor/
2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. exp Surgery/
5. surg*.mp.
6. su.fs.
7. 4 or 5 or 6
8. (debulk* or cytoeduc*).mp.



9. 3 and 7 and 8
10. exp Controlled Clinical Trial/
11. crossover procedure/
12. double-blind procedure/
13. randomized controlled trial/
14. single-blind procedure/
15. random*.mp.
16. factorial*.mp.
17. (crossover* or cross over* or cross-over*).mp.
18. placebo*.mp.
19. (double* adj blind*).mp.
20. (singl* adj blind*).mp.
21. assign*.mp.
22. allocat*.mp.
23. volunteer*.mp.
24. exp cohort analysis/
25. cohort*.mp.
26. series.mp.
27. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 9 and 27

Note

Search performed by Jane Hayes, Information Manager, Cochrane Gynaecologic, Neuro-oncology and Orphan Cancer Group (update of Elattar 2011 up to 2015 Jan week 2, 2015; search amended)

Database**CENTRAL****Date**

16-01-2015

Search Strategy

1. MeSH descriptor Ovarian Neoplasms explode all trees
2. ovar* near/5 cancer*
3. ovar* near/5 neoplas*
4. ovar* near/5 carcinom*
5. ovar* near/5 malignan*



6. ovar* near/5 tumor*
7. ovar* near/5 tumour*
8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9. MeSH descriptor Surgical Procedures, Operative explode all trees
10. surg*
11. Any MeSH descriptor with qualifier: SU
12. (#9 OR #10 OR #11)
13. debulk*
14. cytoreduc*
15. (#13 OR #14)
16. (#8 AND #12 AND #15)

Note Search performed by Jane Hayes, Information Manager, Cochrane Gynaecologic, Neuro-oncology and Orphan Cancer Group (update of Elattar 2011 up to Issue 1, 2015)

3.7.2. RCTs and comparative observational studies – Update Ang et al.

Database	Medline OVID (including PreMEDLINE)
Date	16-01-2015
Search Strategy	<ol style="list-style-type: none">1. exp Ovarian Neoplasms/2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.3. 1 or 24. exp Surgical Procedures, Operative/5. surg*.mp.6. surgery.fs.7. 4 or 5 or 68. debulk*.mp.9. cytoreduc*.mp.10. (ultraradical or ultra-radical or ultra radical).mp.11. exp Omentum/12. omentum.mp.13. bowel.mp.14. abdom*.mp.



-
15. exp Spleen/
 16. spleen.mp.
 17. exp Liver/
 18. liver.mp.
 19. exp Diaphragm/
 20. diaphragm*.mp.
 21. exp Lymph Nodes/
 22. (lymph adj node*).mp.
 23. exp Peritoneum/
 24. peritone*.mp.
 25. exp Urinary Tract/
 26. (urinary adj tract).mp.
 27. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
 28. 7 and 27
 29. exp Splenectomy/
 30. splenectomy.mp.
 31. exp Hysterectomy/
 32. (abdom* adj5 hysterectomy).mp.
 33. abdominohysterectomy.mp.
 34. exp Lymph Node Excision/
 35. (lymph adj node adj excision).mp.
 36. (bilateral adj salpingo adj oophorectomy).mp.
 37. omentectomy.mp.
 38. exp Surgical Stomas/
 39. stoma.mp.
 40. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
 41. 28 or 40
 42. 3 and 41
 43. "randomized controlled trial".pt.
 44. "controlled clinical trial".pt.
 45. randomized.ab.
 46. randomly.ab.
-



47. trial.ab.
48. groups.ab.
49. exp Cohort Studies/
50. cohort*.mp.
51. (case adj series).mp.
52. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 42 and 52
54. Animals/
55. Humans/
56. 54 not (54 and 55)
57. 53 not 56

Note

Search performed by Jane Hayes, Information Manager, Cochrane Gynaecologic, Neuro-oncology and Orphan Cancer Group (update of Ang 2011 up to Jan week 2, 2015)

Database**Embase OVID****Date**

16-01-2015

Search Strategy

1. exp Ovary Tumor/
2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. exp Surgery/
5. surg*.mp.
6. su.fs.
7. 4 or 5 or 6
8. debulk*.mp.
9. cytoreduc*.mp.
10. (ultraradical or ultra-radical or ultra radical).mp.
11. exp Omentum/
12. omentum.mp.
13. bowel.mp.



-
14. abdom*.mp.
 15. exp Spleen/
 16. spleen.mp.
 17. exp Liver/
 18. liver.mp.
 19. exp Diaphragm/
 20. diaphragm*.mp.
 21. exp Lymph Node/
 22. (lymph adj node).mp.
 23. exp Peritoneum/
 24. peritone*.mp.
 25. exp Urinary Tract/
 26. (urinary adj tract).mp.
 27. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
 28. 7 and 27
 29. exp Splenectomy/
 30. splenectomy.mp.
 31. exp Hysterectomy/
 32. (abdom* adj5 hysterectomy).mp.
 33. abdominohysterectomy.mp.
 34. exp Lymphadenectomy/
 35. (lymph adj node adj excision).mp.
 36. (bilateral adj salpingo adj oophorectomy).mp.
 37. omentectomy.mp.
 38. exp Stoma/
 39. stoma.mp.
 40. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
 41. 28 or 40
 42. 3 and 41
 43. exp Controlled Clinical Trial/
 44. randomized.ab.
 45. randomly.ab.
-



- 46. trial.ab.
- 47. groups.ab.
- 48. exp Cohort Analysis/
- 49. cohort*.mp.
- 50. (case adj series).mp.
- 51. 50 or 49 or 46 or 45 or 43 or 44 or 48 or 47
- 52. 42 and 51
- 53. exp Animal/
- 54. Human/
- 55. 53 not (53 and 54)
- 56. 52 not 55

Note

Search performed by Jane Hayes, Information Manager, Cochrane Gynaecologic, Neuro-oncology and Orphan Cancer Group (update of Ang 2011 up to 2015 Jan week 2)

Database**CENTRAL****Date**

16-01-2015

Search Strategy

- 1. MeSH descriptor Ovarian Neoplasms explode all trees
- 2. ovar* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)
- 3. (#1 OR #2)
- 4. MeSH descriptor Surgical Procedures, Operative explode all trees
- 5. surg*
- 6. Any MeSH descriptor with qualifier: SU
- 7. (#4 OR #5 OR #6)
- 8. debulk*
- 9. cytoreduc*
- 10. ultraradical or ultra-radical or ultra radical
- 11. MeSH descriptor Omentum explode all trees
- 12. omentum
- 13. bowel



-
14. abdom*
 15. MeSH descriptor Spleen explode all trees
 16. spleen
 17. MeSH descriptor Liver explode all trees
 18. liver
 19. MeSH descriptor Diaphragm explode all trees
 20. diaphragm*
 21. MeSH descriptor Lymph Nodes explode all trees
 22. lymph next node*
 23. MeSH descriptor Peritoneum explode all trees
 24. peritone*
 25. MeSH descriptor Urinary Tract explode all trees
 26. urinary next tract
 27. (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR 23 OR #24 OR #25 OR #26)
 28. (#7 AND #27)
 29. MeSH descriptor Splenectomy explode all trees
 30. splenectomy
 31. MeSH descriptor Hysterectomy explode all trees
 32. abdom* near/5 hysterectomy
 33. abdominohysterectomy
 34. MeSH descriptor Lymph Node Excision explode all trees
 35. lymph next node next excision
 36. bilateral next salpingo next oophorectomy
 37. omentectomy
 38. MeSH descriptor Surgical Stomas explode all trees
 39. stoma
 40. (#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)
 41. (#28 OR #40)
 42. (#3 AND #41)
-



Note	Search performed by Jane Hayes, Information Manager, Cochrane Gynaecologic, Neuro-oncology and Orphan Cancer Group (update of Ang 2011 up to Issue 1, 2015)
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3.8. Neo-adjuvant chemotherapy and interval debulking versus upfront surgery

3.8.1. Systematic reviews

Database	Medline
Date	13-01-2015
Search Strategy	<div>11 meta-analysis.mp,pt. or review.pt. or search:.tw. (2070030)</div> <div>12 (ovar\$ adj5 neoplas\$).tw. (2788)</div> <div>13 (ovar\$ adj5 cancer\$).tw. (38175)</div> <div>14 (ovar\$ adj5 carcin\$).tw. (16733)</div> <div>15 (ovar\$ adj5 tumo\$).tw. (19875)</div> <div>16 (ovar\$ adj5 metasta\$).tw. (3787)</div> <div>17 (ovar\$ adj5 malig\$).tw. (6363)</div> <div>18 exp Ovarian Neoplasms/ (64515)</div> <div>19 or/12-18 (79952)</div> <div>20 exp Surgical Procedures, Operative/ (2416197)</div> <div>21 surg*.mp. (1479510)</div> <div>22 surgery.fs. (1594742)</div> <div>23 20 or 21 or 22 (3370799)</div> <div>24 debulk*.mp. (4471)</div> <div>25 cytoreduc*.mp. (5478)</div> <div>26 24 or 25 (9393)</div> <div>27 23 and 26 (7986)</div> <div>28 19 and 27 (2920)</div> <div>29 exp Chemotherapy, Adjuvant/ (30217)</div> <div>30 exp Antineoplastic Combined Chemotherapy Protocols/ (106512)</div> <div>31 exp Antineoplastic Agents/ (828285)</div> <div>32 chemother*.mp. (316565)</div> <div>33 exp Drug Therapy/ (1058527)</div> <div>34 exp Drug Therapy, Combination/ (260471)</div>



35	or/29-34 (1785863)
36	28 and 35 (2178)
37	11 and 36 (525)
38	limit 37 to yr="2010 - 2015" (146)

Database	PreMedline																																								
Date	13-01-2015																																								
Search Strategy	<table><tr><td>11</td><td>meta-analysis.mp,pt. or review.pt. or search:.tw. (53276)</td></tr><tr><td>12</td><td>(ovar\$ adj5 neoplas\$).tw. (171)</td></tr><tr><td>13</td><td>(ovar\$ adj5 cancer\$).tw. (3251)</td></tr><tr><td>14</td><td>(ovar\$ adj5 carcin\$).tw. (1007)</td></tr><tr><td>15</td><td>(ovar\$ adj5 tumo\$).tw. (1413)</td></tr><tr><td>16</td><td>(ovar\$ adj5 metasta\$).tw. (350)</td></tr><tr><td>17</td><td>(ovar\$ adj5 malig\$).tw. (474)</td></tr><tr><td>19</td><td>or/12-17 (4648)</td></tr><tr><td>21</td><td>surg*.mp. (103763)</td></tr><tr><td>22</td><td>surgery.fs. (0)</td></tr><tr><td>23</td><td>21 or 22 (103763)</td></tr><tr><td>24</td><td>debulk*.mp. (431)</td></tr><tr><td>25</td><td>cytoreduc*.mp. (472)</td></tr><tr><td>26</td><td>24 or 25 (858)</td></tr><tr><td>27</td><td>23 and 26 (663)</td></tr><tr><td>28</td><td>19 and 27 (227)</td></tr><tr><td>32</td><td>chemother*.mp. (20805)</td></tr><tr><td>36</td><td>28 and 32 (168)</td></tr><tr><td>37</td><td>11 and 36 (11)</td></tr><tr><td>38</td><td>limit 37 to yr="2010 - 2015" (9)</td></tr></table>	11	meta-analysis.mp,pt. or review.pt. or search:.tw. (53276)	12	(ovar\$ adj5 neoplas\$).tw. (171)	13	(ovar\$ adj5 cancer\$).tw. (3251)	14	(ovar\$ adj5 carcin\$).tw. (1007)	15	(ovar\$ adj5 tumo\$).tw. (1413)	16	(ovar\$ adj5 metasta\$).tw. (350)	17	(ovar\$ adj5 malig\$).tw. (474)	19	or/12-17 (4648)	21	surg*.mp. (103763)	22	surgery.fs. (0)	23	21 or 22 (103763)	24	debulk*.mp. (431)	25	cytoreduc*.mp. (472)	26	24 or 25 (858)	27	23 and 26 (663)	28	19 and 27 (227)	32	chemother*.mp. (20805)	36	28 and 32 (168)	37	11 and 36 (11)	38	limit 37 to yr="2010 - 2015" (9)
11	meta-analysis.mp,pt. or review.pt. or search:.tw. (53276)																																								
12	(ovar\$ adj5 neoplas\$).tw. (171)																																								
13	(ovar\$ adj5 cancer\$).tw. (3251)																																								
14	(ovar\$ adj5 carcin\$).tw. (1007)																																								
15	(ovar\$ adj5 tumo\$).tw. (1413)																																								
16	(ovar\$ adj5 metasta\$).tw. (350)																																								
17	(ovar\$ adj5 malig\$).tw. (474)																																								
19	or/12-17 (4648)																																								
21	surg*.mp. (103763)																																								
22	surgery.fs. (0)																																								
23	21 or 22 (103763)																																								
24	debulk*.mp. (431)																																								
25	cytoreduc*.mp. (472)																																								
26	24 or 25 (858)																																								
27	23 and 26 (663)																																								
28	19 and 27 (227)																																								
32	chemother*.mp. (20805)																																								
36	28 and 32 (168)																																								
37	11 and 36 (11)																																								
38	limit 37 to yr="2010 - 2015" (9)																																								



Database	Embase
Date	13-01-2015
Search Strategy	<p>#1. (ovar* NEAR/5 neoplas*):ab,ti OR (ovar* NEAR/5 cancer*):ab,ti OR (ovar* NEAR/5 carcin*):ab,ti OR (ovar* NEAR/5 tumo*):ab,ti OR (ovar* NEAR/5 metasta*):ab,ti OR (ovar* NEAR/5 malig*):ab,ti (85836)</p> <p>#2. 'ovary cancer'/exp (79565)</p> <p>#3. #1 OR #2 (109571)</p> <p>#4. 'antineoplastic agent'/exp OR 'cancer chemotherapy'/exp OR 'cancer combination chemotherapy'/exp OR 'combination chemotherapy'/exp (1584539)</p> <p>#5. 'cytoreductive surgery'/exp (7174)</p> <p>#6. debulk*:ab,ti (7145)</p> <p>#7. #5 or #6 (12234)</p> <p>#8. #3 AND #4 AND #7 (2939)</p> <p>#9. #8 AND AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2010-2015]/py (22)</p>

Database	Cochrane Library
Date	13-01-2015
Search Strategy	<p>#1 (ovar* and (neoplas* or cancer\$ or tumo* or carcin* or metasta* or malig*)):ti,ab</p> <p>#2 MeSH descriptor: [Ovarian Neoplasms] 1 tree(s) exploded</p> <p>#3 #1 or #2</p> <p>#4 MeSH descriptor: [Surgical Procedures, Operative] 1 tree(s) exploded</p> <p>#5 surg*:ti,ab</p> <p>#6 #4 or #5</p> <p>#7 (debulk* or cytoreduc*):ti,ab</p> <p>#8 #6 and #7</p> <p>#9 MeSH descriptor: [Chemotherapy, Adjuvant] 1 tree(s) exploded</p> <p>#10 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] 1 tree(s) exploded</p> <p>#11 MeSH descriptor: [Antineoplastic Agents] 1 tree(s) exploded</p> <p>#12 MeSH descriptor: [Drug Therapy] 1 tree(s) exploded</p> <p>#13 MeSH descriptor: [Drug Therapy, Combination] 1 tree(s) exploded</p>



#14	chemother*.ti,ab
#15	#9 or #10 or #11 or #12 or #13 or #14
#16	#3 and #8 and #15

3.8.2. RCTs

Database	Medline
Date	13-01-2015
Search Strategy	<ol style="list-style-type: none">1 randomized controlled trial.pt. (380225)2 controlled clinical trial.pt. (88313)3 randomized.ab. (279149)4 placebo.ab. (147367)5 clinical trials as topic.sh. (170168)6 randomly.ab. (198174)7 trial.ti. (120096)8 1 or 2 or 3 or 4 or 5 or 6 or 7 (871418)9 exp animals/ not humans.sh. (3967499)10 8 not 9 (799334)12 (ovar\$ adj5 neoplas\$).tw. (2788)13 (ovar\$ adj5 cancer\$).tw. (38175)14 (ovar\$ adj5 carcin\$).tw. (16733)15 (ovar\$ adj5 tumo\$).tw. (19875)16 (ovar\$ adj5 metasta\$).tw. (3787)17 (ovar\$ adj5 malig\$).tw. (6363)18 exp Ovarian Neoplasms/ (64515)19 or/12-18 (79952)20 exp Surgical Procedures, Operative/ (2416197)21 surg*.mp. (1479510)22 surgery.fs. (1594742)23 20 or 21 or 22 (3370799)24 debulk*.mp. (4471)25 cytoreduc*.mp. (5478)



26	24 or 25 (9393)
27	23 and 26 (7986)
28	19 and 27 (2920)
29	exp Chemotherapy, Adjuvant/ (30217)
30	exp Antineoplastic Combined Chemotherapy Protocols/ (106512)
31	exp Antineoplastic Agents/ (828285)
32	chemother*.mp. (316565)
33	exp Drug Therapy/ (1058527)
34	exp Drug Therapy, Combination/ (260471)
35	or/29-34 (1785863)
36	28 and 35 (2178)
39	10 and 36 (341)
41	limit 39 to yr="2011 - 2015" (61)

Comment	The search was updated on September 1 st 2015 and yielded 10 new hits.
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Database	PreMedline
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Date	13-01-2015
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Search Strategy	1 randomized controlled trial.pt. (940)
	2 controlled clinical trial.pt. (99)
	3 randomized.ab. (26074)
	4 placebo.ab. (9424)
	6 randomly.ab. (23362)
	7 trial.ti. (10972)
	8 1 or 2 or 3 or 4 or 6 or 7 (55274)
	12 (ovar\$ adj5 neoplas\$).tw. (171)
	13 (ovar\$ adj5 cancer\$).tw. (3251)
	14 (ovar\$ adj5 carcin\$).tw. (1007)
	15 (ovar\$ adj5 tumo\$).tw. (1413)
	16 (ovar\$ adj5 metasta\$).tw. (350)
	17 (ovar\$ adj5 malig\$).tw. (474)



19 or/12-17 (4648)
21 surg*.mp. (103763)
22 surgery.fs. (0)
23 21 or 22 (103763)
24 debulk*.mp. (431)
25 cytoreduc*.mp. (472)
26 24 or 25 (858)
27 23 and 26 (663)
28 19 and 27 (227)
32 chemother*.mp. (20805)
36 28 and 32 (168)
39 8 and 36 (22)
41 limit 39 to yr="2011 - 2015" (12)

Comment The search was updated on September 1st 2015 and yielded 11 new hits.

Database	Embase
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Date	13-01-2015
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Search Strategy	#1. (ovar* NEAR/5 neoplas*):ab,ti OR (ovar* NEAR/5 cancer*):ab,ti OR (ovar* NEAR/5 carcin*):ab,ti OR (ovar* NEAR/5 tumo*):ab,ti OR (ovar* NEAR/5 metasta*):ab,ti OR (ovar* NEAR/5 malig*):ab,ti (85836) #2. 'ovary cancer'/exp (79565) #3. #1 OR #2 (109571) #4. 'antineoplastic agent'/exp OR 'cancer chemotherapy'/exp OR 'cancer combination chemotherapy'/exp OR 'combination chemotherapy'/exp (1584539) #5. 'cytoreductive surgery'/exp (7174) #6. debulk*:ab,ti (7145) #7. #5 or #6 (12234) #8. #3 AND #4 AND #7 (2939) #9. #8 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2011-2015]/py (31)
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Comment	The search was updated on September 1 st 2015 and yielded 3 new hits.
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Database	Cochrane Library	
Date	13-01-2015	
Search Strategy	#1	(ovar* and (neoplas* or cancer\$ or tumo* or carcin* or metasta* or malig*)):ti,ab
	#2	MeSH descriptor: [Ovarian Neoplasms] 1 tree(s) exploded
	#3	#1 or #2
	#4	MeSH descriptor: [Surgical Procedures, Operative] 1 tree(s) exploded
	#5	surg*:ti,ab
	#6	#4 or #5
	#7	(debulk* or cytoreduc*):ti,ab
	#8	#6 and #7
	#9	MeSH descriptor: [Chemotherapy, Adjuvant] 1 tree(s) exploded
	#10	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] 1 tree(s) exploded
	#11	MeSH descriptor: [Antineoplastic Agents] 1 tree(s) exploded
	#12	MeSH descriptor: [Drug Therapy] 1 tree(s) exploded
	#13	MeSH descriptor: [Drug Therapy, Combination] 1 tree(s) exploded
	#14	chemother*:ti,ab
	#15	#9 or #10 or #11 or #12 or #13 or #14
	#16	#3 and #8 and #15
Comment	The search was updated on September 1 st 2015 and yielded 15 new hits.	



3.9. Intra-peritoneal chemotherapy

Database	Cochrane Database of Systematic Reviews	
Date	24/02/15 09:27:29.119	
Search strategy		
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees	1409
#2	ovar* near/5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcino* or adenocarcino* or metasta*):ab,ti	3200
#3	#1 or #2	3376
#4	MeSH descriptor: [Infusions, Parenteral] explode all trees	11003
#5	MeSH descriptor: [Injections, Intraperitoneal] explode all trees	211
#6	intraperitoneal:ab,ti	1118
#7	intra-peritoneal:ab,ti	48
#8	peritone*:ab,ti	2618
#9	regional:ab,ti	7099
#10	parenteral:ab,ti	5406
#11	#4 or #5 or #6 or #7 or #8 or #9 or #10	26013
#12	carboplatin:ab,ti	2306
#13	MeSH descriptor: [Carboplatin] explode all trees	1008
#14	cisplatin:ab,ti	6143
#15	paclitaxel:ab,ti	2942
#16	MeSH descriptor: [Paclitaxel] explode all trees	1523
#17	doxorubicin:ab,ti	3002
#18	Any MeSH descriptor with qualifier(s): [Drug therapy - DT]	170443
#19	MeSH descriptor: [Antineoplastic Agents] explode all trees	10377



#20	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees	11117
#21	MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees	3379
#22	chemotherap*:ab,ti	26623
#23	#12 or #13 or #14 or #15 or #17 or #18 or #19 or #20 or #21 or #22	192066
#24	#11 and #23	8832
#25	#3 and #24	336
#26	#3 and #24 Publication Year from 2011 to 2014	90
Notes	<i>Details results among databases:</i> SR: 10 CENTRAL: 74 HTA: 5 DARE:1	

Database	Medline OvidSP	
Date	2015-02-23	
Search strategy		
1	exp Ovarian Neoplasms/	65067
2	(ovar* adj5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcin* or adenocarcin* or metastas*)).tw.	67987
3	1 or 2	85673
4	Injections, Intraperitoneal/	28470
5	(intraperitoneal or intra-peritoneal).tw.	60125
6	peritone*.tw.	94623
7	regional.tw.	183004
8	parenteral.tw.	42061



9	exp Infusions, Parenteral/	82561
10	intraabdominal.tw.	6951
11	intra-abdominal.tw.	16189
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	478577
13	carboplatin*.ab,ti.	11002
14	exp carboplatin/	9242
15	paclitaxel*.ab,ti.	19027
16	exp paclitaxel/	19862
17	dt.fs.	1737201
18	exp Antineoplastic Agents/	833941
19	exp chemotherapy/	1065821
20	chemotherap*.ab,ti.	282468
21	cisplatin.ab,ti.	42948
22	doxorubicin.ab,ti.	28932
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2848347
24	12 and 23	174927
25	3 and 24	4454
26	limit 25 to yr="2011 -Current"	970
27	limit 26 to systematic reviews	23
28	randomized controlled trial.pt.	384788
29	controlled clinical trial.pt.	88618
30	randomized.ti,ab.	331574
31	placebo.ti,ab.	162525



32	clinical trials as topic/	170815
33	randomly.ti,ab.	224770
34	trial?.ti.	180986
35	28 or 29 or 30 or 31 or 32 or 33 or 34	957861
36	exp animal/ not humans/	3986356
37	35 not 36	883692
38	26 and 37	124
Notes	<p>23 systematic reviews 124 RCT Filter for systematic reviews: NLM http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html</p> <p>Filter for RCT: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) http://handbook.cochrane.org/chapter_6/box_6.4.d_cochrane_hsss_2008_sensprec_oid.htm</p>	



Database	Embase	
Date	2015-02-24	
Search strategy		
1	'ovary tumor'/exp	104815
2	(ovar* NEAR/5 (cancer* OR tumor* OR tumour* OR neoplas* OR carcin* OR adenocarcin* OR malignan* OR metastas*)) :ab,ti	88010
3	#1 OR #2	121107
4	'infusion'/exp	88565
5	'intraperitoneal drug administration'/de	110454
6	intraperitoneal:ab,ti	71843
7	'intra peritoneal':ab,ti	2210
8	peritone*:ab,ti	117098
9	regional:ab,ti	238405
10	parenteral:ab,ti	55368
11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	638229
12	carboplatin*:ab,ti	17046
13	'carboplatin'/exp	46667
14	paclitaxel:ab,ti	28435
15	'paclitaxel'/exp	70605
16	'paclitaxel derivative'/exp	718
17	'paclitaxel trevatide'/exp	0
18	'paclitaxel tocosol'/exp	24
19	'paclitaxel poliglumex'/exp	306
20	'antineoplastic agent'/exp	1544121



21	'antineoplastic agent'/exp	1544121
22	chemotherap*:ab,ti	408112
23	cisplatin:ab,ti	57442
24	doxorubicin:ab,ti	37472
25	'drug therapy':lnk	3018373
26	'chemotherapy'/exp	424221
27	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	3971314
28	#11 AND #27	152724
29	#3 AND #28	6995
30	#3 AND #28 AND [2011-2015]/py	2355
31	[medline]/lim	21664157
32	#30 NOT #31	1427
33	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	192672
34	#32 AND #33	20
35	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1167015
36	#32 AND #35	182

Notes

20 systematic reviews

182 RCT

Overlap with Medline excluded.

SR search filter:

RCT search filter:

Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association : JMLA. 2006 Jan;94(1):41-7



3.10. First-line weekly (dose dense) chemotherapy

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>	
Date	2015-04-16	
Search strategy		
1	exp ovarian neoplasms/	65867
2	(ovar* adj5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcin* or adenocarcin* or metasta*)).ab,ti.	69007
3	1 or 2	86816
4	carboplatin*.ab,ti.	11164
5	exp carboplatin/	9376
6	paclitaxel*.ab,ti.	19411
7	exp paclitaxel/	20174
8	dt.fs.	1758489
9	exp Antineoplastic Agents/	843443
10	exp chemotherapy/	1077341
11	chemotherap*.ab,ti.	286974
12	cisplatin.ab,ti.	43688
13	doxorubicin.ab,ti.	29393
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	2881614
15	3 and 14	28923
16	dose-dense.ab,ti.	657
17	weekly.ab,ti.	76686
18	"dose dense".ab,ti.	657



76	Ovarian cancer: diagnosis, treatment and follow-up	KCE Report 268S
19	"dose density".ab,ti.	136
20	(every adj3 week?).ab,ti.	25203
21	((sequential or reccurent or interval or aggressive or scheduled or regimen? or cycle? or weekly) adj3 (therapy or therapies or chemotherapy or chemotherapies or treatment or dose?)).ab,ti.	109038
22	"once a week".ab,ti.	7039
23	monthly.ab,ti.	38991
24	bimonthly.ab,ti.	1118
25	(each adj3 week?).ab,ti.	12584
26	pk.fs.	243125
27	ad.fs.	1141350
28	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	1482266
29	15 and 28	10252
30	exp animal/ not humans/	4021057
31	29 not 30	9896
32	limit 31 to systematic reviews	153
33	randomized controlled trial.pt.	391172
34	controlled clinical trial.pt.	89152
35	randomized.ti,ab.	338664
36	placebo.ti,ab.	165344
37	clinical trials as topic/	172108
38	randomly.ti,ab.	228633
39	trial?.ti.	185032
40	33 or 34 or 35 or 36 or 37 or 38 or 39	973161
41	exp animal/ not humans/	4021057



42	40 not 41	898020
43	29 and 42	2087
44	limit 43 to yr="1990 -Current"	1786
45	editorial.pt.	374482
46	(letter not comment).pt.	518333
47	45 or 46	892761
48	44 not 47	1757

Notes

Database	Embase	
Date	2015-04-15	
Search strategy		
1	'ovary tumor'/exp	106031
2	(ovar* NEAR/5 (cancer* OR tumor* OR tumour* OR neoplas* OR carcin* OR adenocarcin* OR malignan* OR metastas*)) :ab,ti	89615
3	#1 OR #2	123142
4	carboplatin*:ab,ti	17289
5	'carboplatin'/exp	47261
6	paclitaxel:ab,ti	28938
7	'paclitaxel'/exp	71549
8	'paclitaxel derivative'/exp	718
9	'paclitaxel trevatide'/exp	0
10	'paclitaxel tocosol'/exp	24
11	'paclitaxel poliglumex'/exp	309



78	Ovarian cancer: diagnosis, treatment and follow-up	KCE Report 268S
12	'antineoplastic agent'/exp	1562702
13	chemotherap*:ab,ti	414804
14	cisplatin:ab,ti	58284
15	doxorubicin:ab,ti	37993
16	'drug therapy':lnk	3047229
17	'chemotherapy'/exp	431611
18	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	4014468
19	#3 AND #18	52974
20	'dose dense':ab,ti	1234
21	weekly:ab,ti	109840
22	'dose dense':ab,ti	1234
23	'dose density':ab,ti	227
24	(every NEAR/3 week*):ab,ti	39338
25	((sequential OR recurrent OR interval OR aggressive OR scheduled OR regimen OR regimens OR cycle OR cycles OR weekly) NEAR/3 (therapy OR therapies OR chemotherapy OR chemotherapies OR treatment OR dose OR doses)):ab,ti	156110
26	'once a week':ab,ti	10167
27	monthly:ab,ti	56864
28	bimonthly:ab,ti	1487
29	(each NEAR/3 week*):ab,ti	18227
30	'pharmacokinetics'/exp	558966
31	'drug administration':lnk	1335385
32	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	2039755
33	#19 AND #32	17652
34	[medline]/lim	21944312



35	#33 NOT #34	4565
36	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	198629
37	#35 AND #36	116
38	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1184756
39	#35 AND #38	701
40	#39 NOT #37	650
41	#39 NOT #37 AND [1990-2015]/py	648

Date	Cochrane Database of Systematic Reviews	
Database	15/04/15 22:34:11.491	
Search Strategy	#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees 1413
	#2	(ovar* near/5 (cancer* or neoplas* or malignan* or tumor* or tumour* or carcin* or adenocarcin* or metasta*)):ab,ti 3053
	#3	#1 or #2 3244
Note	64 Systematic reviews in Cochrane about ovarian neoplasms. It's a small enough number to avoid further refinement.	



3.11. Routine Ca 125 measurement during follow-up

3.11.1. Systematic reviews

Database	Medline
Date	27-01-2015
Search Strategy	<ol style="list-style-type: none">1 (ovar\$ adj5 neoplas\$).tw. (2793)2 (ovar\$ adj5 cancer\$).tw. (38311)3 (ovar\$ adj5 carcin\$).tw. (16771)4 (ovar\$ adj5 tumo\$).tw. (19913)5 (ovar\$ adj5 metasta\$).tw. (3800)6 (ovar\$ adj5 malig\$).tw. (6374)7 exp Ovarian Neoplasms/ (64652)8 or/1-7 (80138)9 ca-125 antigen/ (3596)10 Tumor Markers, Biological/ (89032)11 (CA125 or CA-125 or (cancer adj3 antigen adj "125") or ((tumor or tumour) adj marker\$)).ti,ab. (19322)12 or/9-11 (100289)13 early diagnosis/ or "early detection of cancer"/ (22772)14 ((serial adj5 monitoring) or (assessing adj follow*) or (recurrent adj5 disease?) or follow-up or re-evaluated or (monitoring adj5 recurr*)).ti,ab. (605675)15 Follow-Up Studies/ or exp Longitudinal Studies/ (580504)16 neoplasm recurrence, local/ or neoplasm, residual/ (90351)17 Recurrence/ (147829)18 (recurren* or residual or relaps*).ti,ab. (561195)19 13 or 14 or 15 or 16 or 17 or 18 (1445056)20 8 and 12 and 19 (2787)21 limit 20 to yr="2010 - 2015" (876)22 meta-analysis.mp,pt. or review.pt. or search:.tw. (2074518)23 21 and 22 (121)



Database	PreMedline
Date	27-01-2015
Search Strategy	<ol style="list-style-type: none">1 (ovar\$ adj5 neoplas\$).tw. (176)2 (ovar\$ adj5 cancer\$).tw. (3227)3 (ovar\$ adj5 carcin\$).tw. (996)4 (ovar\$ adj5 tumo\$).tw. (1416)5 (ovar\$ adj5 metasta\$).tw. (342)6 (ovar\$ adj5 malig\$).tw. (479)8 or/1-6 (4621)11 (CA125 or CA-125 or (cancer adj3 antigen adj "125") or ((tumor or tumour) adj marker\$)).ti,ab. (1396)14 ((serial adj5 monitoring) or (assessing adj follow*) or (recurrent adj5 disease?) or follow-up or re-evaluated or (monitoring adj5 recurr*)).ti,ab. (49622)18 (recurren* or residual or relaps*).ti,ab. (47248)19 14 or 18 (86576)20 8 and 11 and 19 (113)21 limit 20 to yr="2010 - 2015" (87)22 meta-analysis.mp,pt. or review.pt. or search:.tw. (53038)23 21 and 22 (5)

Database	Embase
Date	27-01-2015
Search Strategy	<ol style="list-style-type: none">#1. (ovar* NEAR/5 neoplas*):ab,ti OR (ovar* NEAR/5 cancer*):ab,ti OR (ovar* NEAR/5 carcin*):ab,ti OR (ovar* NEAR/5 tumo*):ab,ti OR (ovar* NEAR/5 metasta*):ab,ti OR (ovar* NEAR/5 malig*):ab,ti OR 'ovary cancer'/exp (109792)#2. 'ca 125 antigen'/exp OR 'tumor antigen'/de (38399)#3. ca125:ab,ti OR 'ca 125':ab,ti OR ((cancer NEAR/3 antigen):ab,ti AND (antigen NEAR/1 '125'):ab,ti) OR (tum??r NEAR/2 marker?):ab,ti (11819)#4. (serial NEAR/5 monitoring):ab,ti OR (assessing NEAR/1 follow*):ab,ti OR (recurrent NEAR/5 disease?):ab,ti OR 'follow up':ab,ti OR 're evaluated':ab,ti OR (monitoring NEAR/5 recurr*):ab,ti OR 'minimal residual disease'/exp OR 'cancer recurrence'/exp OR 'recurrent disease'/exp OR 'tumor recurrence'/exp OR recurren*:ab,ti OR residual:ab,ti OR relaps*:ab,ti OR 'follow up'/exp OR 'longitudinal study'/exp (1915994)



#5. #2 OR #3 (42843)
#6. #1 AND #4 AND #5 (3294)
#7. #6 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2010-2015]/py (11)

Database	Cochrane Library	
Date	27-01-2015	
Search Strategy	#1	(ovar* and (neoplas* or cancer\$ or tumo* or carcin* or metasta* or malig*)):ti,ab
	#2	MeSH descriptor: [Ovarian Neoplasms] 1 tree(s) exploded
	#3	#1 or #2
	#4	(CA125 or CA-125 or (cancer and antigen and "125") or ((tumor or tumour) and marker*)):ti,ab
	#5	MeSH descriptor: [CA-125 Antigen] 1 tree(s) exploded
	#6	MeSH descriptor: [Tumor Markers, Biological] 1 tree(s) exploded
	#7	#4 or #5 or #6
	#8	#3 and #7

3.11.2. Randomized controlled trials

Database	Medline	
Date	27-01-2015	
Search Strategy	1	(ovar\$ adj5 neoplas\$).tw. (2793)
	2	(ovar\$ adj5 cancer\$).tw. (38311)
	3	(ovar\$ adj5 carcin\$).tw. (16771)
	4	(ovar\$ adj5 tumo\$).tw. (19913)
	5	(ovar\$ adj5 metasta\$).tw. (3800)
	6	(ovar\$ adj5 malig\$).tw. (6374)
	7	exp Ovarian Neoplasms/ (64652)
	8	or/1-7 (80138)
	9	ca-125 antigen/ (3596)
	10	Tumor Markers, Biological/ (89032)
	11	(CA125 or CA-125 or (cancer adj3 antigen adj "125") or ((tumor or tumour) adj marker\$)).ti,ab. (19322)



12 or/9-11 (100289)
13 early diagnosis/ or "early detection of cancer"/ (22772)
14 ((serial adj5 monitoring) or (assessing adj follow*) or (recurrent adj5 disease?) or follow-up or re-evaluated or (monitoring adj5 recurr*).ti,ab. (605675)
15 Follow-Up Studies/ or exp Longitudinal Studies/ (580504)
16 neoplasm recurrence, local/ or neoplasm, residual/ (90351)
17 Recurrence/ (147829)
18 (recurren* or residual or relaps*).ti,ab. (561195)
19 13 or 14 or 15 or 16 or 17 or 18 (1445056)
20 8 and 12 and 19 (2787)
21 limit 20 to yr="2010 - 2015" (876)
22 meta-analysis.mp,pt. or review.pt. or search:.tw. (2074518)
23 21 and 22 (121)
24 randomized controlled trial.pt. (381216)
25 controlled clinical trial.pt. (88387)
26 randomized.ab. (280058)
27 placebo.ab. (147683)
28 clinical trials as topic.sh. (170332)
29 randomly.ab. (198880)
30 trial.ti. (120459)
31 24 or 25 or 26 or 27 or 28 or 29 or 30 (873585)
32 exp animals/ not humans.sh. (3972666)
33 31 not 32 (801200)
34 20 and 33 (203)
35 limit 34 to yr="2010 - 2015" (84)

Database	PreMedline
Date	27-01-2015
Search Strategy	1 (ovar\$ adj5 neoplas\$).tw. (176) 2 (ovar\$ adj5 cancer\$).tw. (3227) 3 (ovar\$ adj5 carcin\$).tw. (996)



-
- 4 (ovar\$ adj5 tumo\$).tw. (1416)
 - 5 (ovar\$ adj5 metasta\$).tw. (342)
 - 6 (ovar\$ adj5 malig\$).tw. (479)
 - 8 or/1-6 (4621)
 - 11 (CA125 or CA-125 or (cancer adj3 antigen adj "125") or ((tumor or tumour) adj marker\$)).ti,ab. (1396)
 - 14 ((serial adj5 monitoring) or (assessing adj follow*) or (recurrent adj5 disease?) or follow-up or re-evaluated or (monitoring adj5 recurr*)).ti,ab. (49622)
 - 18 (recurren* or residual or relaps*).ti,ab. (47248)
 - 19 14 or 18 (86576)
 - 20 8 and 11 and 19 (113)
 - 21 limit 20 to yr="2010 - 2015" (87)
 - 24 randomized controlled trial.pt. (692)
 - 25 controlled clinical trial.pt. (81)
 - 26 randomized.ab. (25987)
 - 27 placebo.ab. (9342)
 - 29 randomly.ab. (23154)
 - 30 trial.ti. (10928)
 - 31 24 or 25 or 26 or 27 or 29 or 30 (54893)
 - 34 20 and 31 (8)
 - 35 limit 34 to yr="2010 - 2015" (5)
-

Database	Embase
Date	27-01-2015
Search Strategy	<div>#1. (ovar* NEAR/5 neoplas*):ab,ti OR (ovar* NEAR/5 cancer*):ab,ti OR (ovar* NEAR/5 carcin*):ab,ti OR (ovar* NEAR/5 tumo*):ab,ti OR (ovar* NEAR/5 metasta*):ab,ti OR (ovar* NEAR/5 malig*):ab,ti OR 'ovary cancer'/exp (109792)</div> <div>#2. 'ca 125 antigen'/exp OR 'tumor antigen'/de (38399)</div> <div>#3. ca125:ab,ti OR 'ca 125':ab,ti OR ((cancer NEAR/3 antigen):ab,ti AND (antigen NEAR/1 '125'):ab,ti) OR (tum??r NEAR/2 marker?):ab,ti (11819)</div>



- #4. (serial NEAR/5 monitoring):ab,ti OR (assessing NEAR/1 follow*):ab,ti OR (recurrent NEAR/5 disease?):ab,ti OR 'follow up':ab,ti OR 're evaluated':ab,ti OR (monitoring NEAR/5 recurr*):ab,ti OR 'minimal residual disease'/exp OR 'cancer recurrence'/exp OR 'recurrent disease'/exp OR 'tumor recurrence'/exp OR recurren*:ab,ti OR residual:ab,ti OR relaps*:ab,ti OR 'follow up'/exp OR 'longitudinal study'/exp (1915994)
- #5. #2 OR #3 (42843)
- #6. #1 AND #4 AND #5 (3294)
- #7. #6 AND [randomized controlled trial]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2013-2015]/py (15)

Database	Cochrane Library	
Date	27-01-2015	
Search Strategy	#1	(ovar* and (neoplas* or cancer\$ or tumo* or carcin* or metasta* or malig*)):ti,ab
	#2	MeSH descriptor: [Ovarian Neoplasms] 1 tree(s) exploded
	#3	#1 or #2
	#4	(CA125 or CA-125 or (cancer and antigen and "125") or ((tumor or tumour) and marker*)):ti,ab
	#5	MeSH descriptor: [CA-125 Antigen] 1 tree(s) exploded
	#6	MeSH descriptor: [Tumor Markers, Biological] 1 tree(s) exploded
	#7	#4 or #5 or #6
	#8	#3 and #7



3.12. Patient preferences

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present		
Date	2014-01-07		
Search Strategy	#	Query	Results
	1	exp ovarian neoplasms/	67267
	2	(ovar* adj3 (cancer? or neoplasm? or tumo?r* or carcinoma? or adenocarcinoma?)).ab,ti.	64301
	3	1 or 2	84809
	4	Patient Preference/	3618
	5	Patient Satisfaction/	63207
	6	limit 5 to yr="1997 - 2009"	37917
	7	preference*.mp.	113390
	8	choice*.mp.	267461
	9	preferred.mp.	91792
	10	chosen.mp.	84902
	11	prefer.mp.	14996
	12	prefers.mp.	2918
	13	choose.mp.	28177
	14	chooses.mp.	1254
	15	decided.mp.	20266
	16	decide.mp.	16016
	17	decides.mp.	1555
	18	desire*.mp.	73532



19	decision*.mp.	296491
20	favo?re*.mp.	32588
21	exp decision making/	132715
22	Patient Participation/	19401
23	preferring.mp.	5686
24	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 23	934716
25	6 and 24	8221
26	4 or 22 or 25	30280
27	exp Patients/	72241
28	patient.mp.	1998067
29	patients.mp.	4276694
30	client.mp.	19831
31	clients.mp.	27837
32	inpatient.mp.	48577
33	inpatients.mp.	36611
34	outpatient.mp.	100020
35	outpatients.mp.	42543
36	out#patient.mp.	0
37	out#patients.mp.	0
38	hospitalized.mp.	73703
39	institutionalized.mp.	8743
40	treated.mp.	1261906
41	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	5897385



	42	24 and 41	377889
	43	4 or 22 or 25 or 42	388970
	44	3 and 43	2207
	45	limit 44 to systematic reviews	91
Note	Search for systematic reviews Patients terms joined with preferences terms with AND		

Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present		
Date	2014-01-12		
Search Strategy	#	Query	Results
	1	exp ovarian neoplasms/	67273
	2	(ovar* adj3 (cancer? or neoplasm? or tumo?r* or carcinoma? or adenocarcinoma?)).ab,ti.	64314
	3	1 or 2	84821
	4	Patient Preference/	3623
	5	Patient Satisfaction/	63238
	6	limit 5 to yr="1997 - 2009"	37917
	7	preference*.mp.	113411
	8	choice*.mp.	267514
	9	preferred.mp.	91827
	10	chosen.mp.	84932
	11	prefer.mp.	14998
	12	prefers.mp.	2919
	13	choose.mp.	28183



14	chooses.mp.	1253
15	decided.mp.	20273
16	decide.mp.	16021
17	decides.mp.	1556
18	desire*.mp.	73566
19	decision*.mp.	296621
20	favo?re*.mp.	32609
21	exp decision making/	132706
22	Patient Participation/	19395
23	preferring.mp.	5681
24	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 23	935040
25	6 and 24	8221
26	patient.mp.	1998898
27	patients.mp.	4278177
28	client.mp.	19836
29	clients.mp.	27845
30	inpatient.mp.	48601
31	inpatients.mp.	36623
32	outpatient.mp.	100063
33	outpatients.mp.	42561
34	out#patient.mp.	0
35	out#patients.mp.	0
36	hospitalized.mp.	73726



37	institutionalized.mp.	8740
38	treated.mp.	1262260
39	((preference* or choice* or preferred or chosen or prefer or prefers or choose or chooses or decided or decide or decides or desire* or decision* or favo?re* or preferring) adj3 (patient or patients or client or clients or inpatient or inpatients or outpatient or outpatients or out#patient or out#patients or hospitalized or institutionalized or treated)).mp.	49103
40	4 or 22 or 25 or 39	70668
41	3 and 40	328

Note

Search for all studies

Patients terms joined with preferences terms with proximity operator

Database	Embase (Embase.com)		
Date	2015-01-07		
Search Strategy	#	Query	Results
	#1	'ovary tumor'/exp	103,433
	#2	(ovar* NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)):ab,ti	78,998
	#3	#1 OR #2	115,133
	#4	'patient participation'/de OR 'patient preference'/de OR (choice* OR chosen OR prefer* OR choos* OR decid* OR desire* OR decision* OR favore* OR favoure* OR 'decision making'/exp AND ('patient'/exp OR patient OR patients OR client OR clients OR inpatient OR inpatients OR outpatient OR outpatients OR out?patient OR out?patients OR hospitalized OR institutionalized OR treated))	608,786
	#5	#3 AND #4	4,367



#6	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	187,863
#7	#5 AND #6	129

Note

Database	Embase (Embase.com)		
Date	2015-01-12		
Search Strategy	#	Query	Results
	#1	'ovary tumor'/exp	103,472
	#2	(ovar* NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)) :ab,ti	79,034
	#3	#1 OR #2	115,184
	#4	'patient participation'/de OR 'patient preference'/de OR ((choice* OR chosen OR prefer* OR choos* OR decid* OR desire* OR decision* OR favore* OR favoure*) NEAR/3 (patient OR patients OR client OR clients OR inpatient OR inpatients OR outpatient OR outpatients OR out?patient OR out?patients OR hospitalized OR institutionalized OR treated)) :ab,ti	85,862
	#5	#3 AND #4	562
	#6	[medline]/lim	21,507,037
	#7	#5 NOT #6	232

Note



Database	Cochrane		
Date	2015-01-08		
Search Strategy	#	Query	Results
	#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees	1395
	#2	(ovar* near/3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma*)):ab,ti	2912
	#3	#1 or #2	3111
	#4	MeSH descriptor: [Patient Preference] explode all trees	349
	#5	MeSH descriptor: [Patient Satisfaction] this term only	8661
	#6	#5 Publication Year from 2005 to 2009	2904
	#7	preference*:ab,ti	6280
	#8	choice*:ab,ti	11960
	#9	preferred:ab,ti	6263
	#10	chosen:ab,ti	4398
	#11	prefer:ab,ti	1010
	#12	prefers:ab,ti	15
	#13	choose:ab,ti	1296
	#14	chooses:ab,ti	21
	#15	decided:ab,ti	1102
	#16	decide:ab,ti	697
	#17	decides:ab,ti	25
	#18	desire*:ab,ti	2926
	#19	decision*:ab,ti	9768



#20	favore*:ab,ti or favoure*:ab,ti	2607
#21	MeSH descriptor: [Decision Making] explode all trees	2689
#22	MeSH descriptor: [Patient Participation] explode all trees	874
#23	preferring:ab,ti	211
#24	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #23	42008
#25	#6 and #24	594
#26	#4 or #22 or #25	1759
#27	MeSH descriptor: [Patients] explode all trees	4131
#28	patient:ab,ti	97856
#29	patients:ab,ti	421968
#30	client:ab,ti	1069
#31	clients:ab,ti	1526
#32	inpatient:ab,ti	3969
#33	inpatients:ab,ti	3008
#34	outpatient:ab,ti	10813
#35	outpatients:ab,ti	7458
#36	"out patient":ab,ti or "out-patient":ab,ti	1121
#37	"out patients":ab,ti or "out-patients":ab,ti	1265
#38	hospitalized:ab,ti	5433
#39	institutionalized:ab,ti	546
#40	treated:ab,ti	108753
#41	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40	462843



	#42	#24 and #41	27451
	#43	#4 or #22 or #25 or #42	28240
	#44	#3 and #43	154
Note	Details: CDSR: 11 Central: 137 Methods: 5 Economic evaluations: 1		



4. STUDY SELECTION AND QUALITY APPRAISAL

4.1. Quality appraisal tools

4.1.1. Guidelines

The AGREE II evaluation score was used to critically appraise guidelines retrieved (Table 1).

Table 1 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II

Domain 1. Scope and Purpose

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Domain 2. Stakeholder Involvement

4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.

Domain 3. Rigour of Development

7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.

Domain 4. Clarity of Presentation

15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.



Critical appraisal of clinical practice guidelines - AGREE II

Domain 5. Applicability

18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.

Domain 6. Editorial Independence

22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

4.1.2. Systematic reviews

The AMSTAR checklist was used to assess systematic reviews (Table 2).

Table 2 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	<input type="checkbox"/> Yes <input type="checkbox"/> No



Question	Answer
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	<input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I ²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable



Question	Answer
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable

4.1.3. Diagnostic accuracy studies

For the quality assessment of diagnostic accuracy studies, we used the QUADAS Tool (Table 3).

Table 3 – The QUADAS tool

Item	Label	Yes	No	Unclear	Not applicable
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?				
2.	Were selection criteria clearly described?				
3.	Is the reference standard likely to correctly classify the target condition?				
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?				
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?				
6.	Did patients receive the same reference standard regardless of the index test result?				
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?				
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?				
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?				



Item	Label	Yes	No	Unclear	Not applicable
10.	Were the index test results interpreted without knowledge of the results of the reference standard?				
11.	Were the reference standard results interpreted without knowledge of the results of the index test?				
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?				
13.	Were uninterpretable/ intermediate test results reported?				
14.	Were withdrawals from the study explained?				

4.1.4. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 4).

Table 4 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		



Domain	Support for judgement	Review authors' judgement
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

For the assessment of the quality of comparative observational studies the Cochrane Collaboration's tool for assessing risk of bias was used as well, but with the addition of two extra items that apply to potential bias due to the selection of participants: 'Concurrency of the intervention and comparator group' and 'Comparability of the intervention and comparator group'. For the first item low risk of bias was assigned if the participants in the intervention and comparator group were enrolled and followed-up concurrently (i.e. in parallel). For the second item low risk of bias was assigned in case of a matched study design and/or appropriate adjustment for confounders in the analysis (e.g. age, tumour type, stage, performance status).



4.2. Study selection and quality appraisal

4.2.1. Pre-operative assessment pelvic mass

RCTs, non-randomized comparative studies

On June 15, 2015 a search was performed to identify SRs and primary studies (RCTs and non-randomized comparative studies) regarding the question whether the use of the Risk of Malignancy Index (RMI) to guide treatment decisions in adult patients with a (complex) ovarian mass without signs of advanced disease results in better clinical outcomes.

MEDLINE, Embase, Cochrane Database of Systematic reviews (CDSR), Database of Abstracts of Reviews of Effect (DARE) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception. In total, 475 potentially relevant references were identified (Figure 1). After deduplication, 314 references remained (SRs and primary studies combined). Based on title and abstract 299 references were excluded. The remaining 15 references were all excluded with reason (Table 6).

Diagnostic accuracy studies

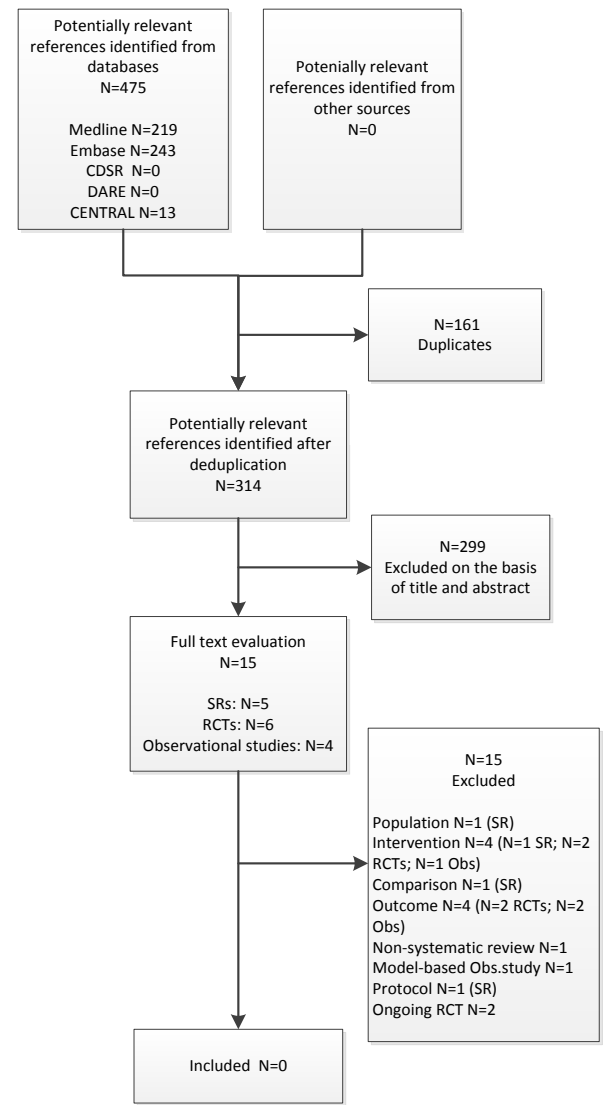
Data on the diagnostic accuracy of RMI and other predictive models were taken from a recent systematic review and meta-analysis.¹ No update was performed. Critical appraisal of the included systematic review is summarized in Table 5.

Table 5 – Methodological quality of the included systematic review (AMSTAR) regarding diagnostic accuracy studies pre-operative assessment pelvic mass

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Kaijser 2014 ¹	yes	yes	yes	yes	no	no	yes	yes	yes	no	no



Figure 1 – PRISMA flowchart selection of primary studies Risk of Malignancy index



**Table 6 – Excluded references Risk of Malignancy index (n=15)**

Reference	Study design	Reason
Chan 2006 ²	SR	Excluded on intervention (RMI not studied as an intervention)
Fung 2004 ³	SR	Excluded on population (asymptomatic postmenopausal women from general population)
Geomini 2011 ⁴	Observational study	Excluded on design (model based study)
Jacobs 1999 ⁵	RCT	Excluded on intervention (no RMI)
Jeyarajah 1999 ⁶	Observational study	Excluded on intervention (no RMI)
Kobayashi 2008 ⁷	RCT	Excluded on intervention (no RMI)
Lockwood 2013 ⁸	SR	Protocol
Menon 2005 ⁹	RCT	Excluded on outcome
Menon 2009 ¹⁰	RCT	Excluded on outcome
Myers 2006 ¹¹	SR	Excluded comparison
Nunes 2012 ¹²	RCT	Protocol / ongoing study
Ozols 2004 ¹³	SR	Excluded on design (non-systematic review)
Sayasneh 2013 ¹⁴	RCT	Ongoing study
Timmerman 2007 ¹⁵	Observational study	Excluded on outcome (accuracy measures, predictive values)
Van Calster 2012 ¹⁶	Observational study	Excluded on outcome (only accuracy outcomes)

4.2.2. Intra-operative frozen section

4.2.2.1. Selection of RCTs

On April 29, 2015 a search was performed to identify RCTs regarding the use of intraoperative frozen section to guide treatment decisions for patients with (presumed) early-stage ovarian cancer. MEDLINE, Embase and CENTRAL were searched from inception.

In total, 94 potentially relevant references were identified (Figure 2). After deduplication 76 references remained. Based on title and abstract all references were excluded.

4.2.2.2. Selection of diagnostic test accuracy studies

On May 5, 2015 a search was performed to identify diagnostic test accuracy studies regarding the use of intraoperative frozen section to guide treatment decisions for patients with (presumed) early-stage ovarian cancer. MEDLINE and Embase were searched from 2009.

In total, 706 potentially relevant references were identified (Figure 3). After deduplication, 509 references remained. Based on title and abstract 488 references were excluded. Of the remaining 21 references, 11 were included, two were already assessed in already included SRs and eight studies were excluded with reason (Table 7).



Figure 2 – Study flow of selection of RCTs frozen section

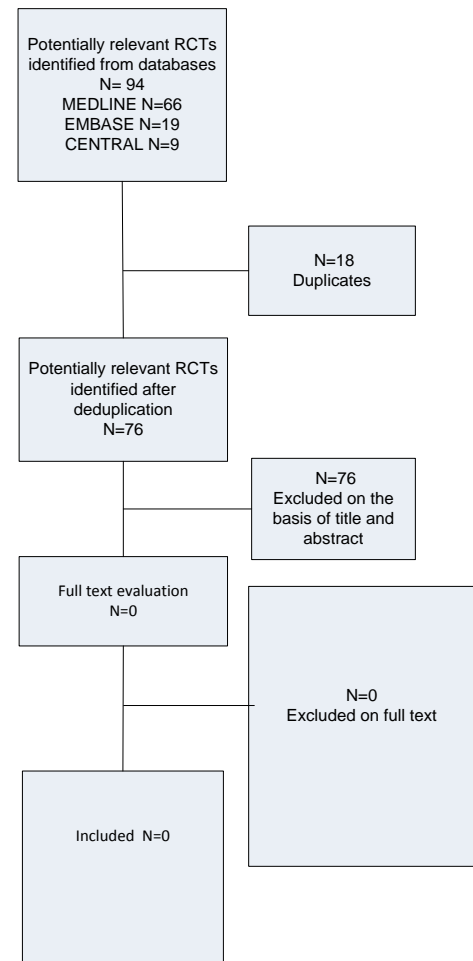
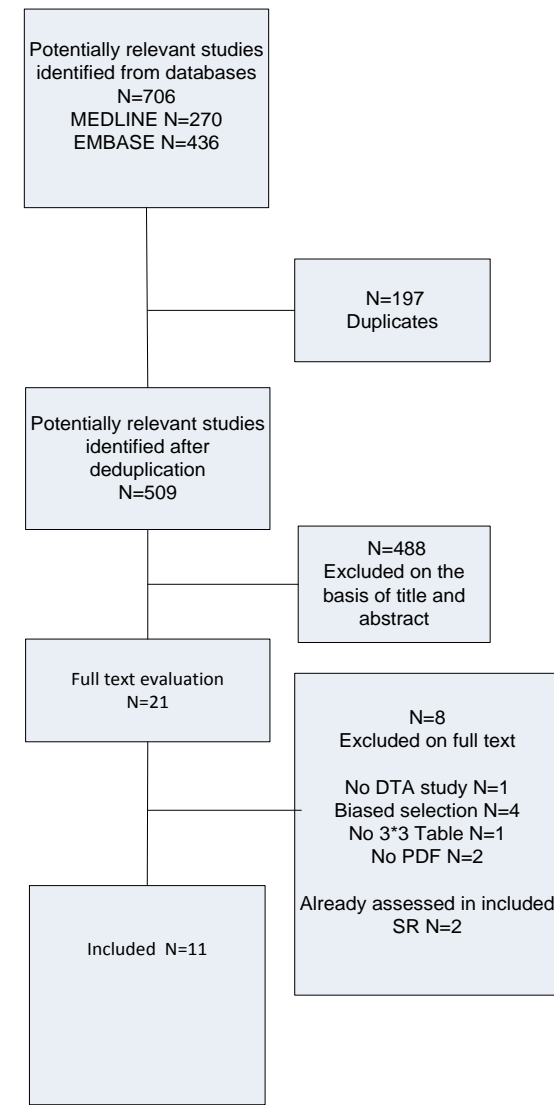


Figure 3 – Study flow of selection of DTA studies frozen section



**Table 7 – Excluded DTA studies frozen section**

Reference	Reasons
Abbasi 2011 ¹⁷	No PDF available
Aslam 2010 ¹⁸	Selection was based on first 400 frozen section positives and 400 frozen section negatives. Sampling fraction must be known to allow unbiased estimates of sensitivity and specificity
Basaran 2014 ¹⁹	(Posthoc) selection of only borderline ovarian tumours
Gultekin 2011 ²⁰	No PDF available / (posthoc) selection of only borderline ovarian tumours
Ouladsahebmadare 2015 ²¹	(Posthoc) exclusion of borderline ovarian tumours
Pongsuvareeyakul 2012²²	(Posthoc) selection of only mucinous tumours
Stewart 2010²³	3 by 3 Tables for frozen section not retrievable
Ureyen 2014 ²⁴	No DTA study / only women with borderline ovarian tumours included

4.2.2.3. Critical appraisal

Systematic reviews

Of the included reviews, quality appraisal through the AMSTAR criteria was performed. Three reviews scored positively on the majority of the items²⁵⁻²⁷, although in two meta-analysis was performed according to methods that are now considered obsolete.^{26, 27} Because meta-analyses can be replicated with state-of-the-art methods, these reviews were further processed. One review scored negatively on almost all AMSTAR items and was excluded.²⁸



Table 8 – Methodological quality of included systematic reviews (AMSTAR) regarding frozen section

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Covens 2012 ²⁵	?	+	(+)	-	+/-	-	+	-	+	-	-
Geomini 2005 ²⁶	?	+	+	-	+	+	+	+	+	+	-
Heatley 2012 ²⁸	?	?	-	-	-	-	-	NA	-	-	-
Medeiros 2005 ²⁷	?	+	+	-	+	+	+	+	+	+	-

NA=not applicable;

* Globally described

** Statistical methods used are now considered obsolete (but primary study results will be used for a replication of a state-of-the art random effects meta-analysis)

*** Complete list available from the authors

Diagnostic test accuracy studies

Of the 11 studies identified in the search update, one scored high risk of bias for Patient Selection and two low risk (Figure 4). Unclear risk of bias was present in four studies for Index Test, in all studies for Reference Standard and in two studies for Flow and Timing. All other studies were considered low risk of bias for those domains (Figure 4). Two studies scored high applicability concerns for Patient Selection, four studies had unclear concerns for one or more applicability domains and the remainder scored low concern.



Figure 4 – Frozen section: summary QUADAS assessment of the 11 newly included diagnostic test accuracy studies

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Acikalin 2014	?	?	?	+	?	?	?
Bige 2011	?	+	?	+	-	+	+
Cross 2012	+	+	?	+	+	+	+
Gorisek 2009	?	?	?	?	?	?	+
Ilker 2011	-	+	?	+	-	+	+
Kokka 2009	+	?	?	+	+	+	+
Malipatil 2013	?	+	?	+	?	+	+
Rakhshan 2009	?	+	?	+	?	+	+
Subbian 2013	?	+	?	?	+	+	+
Sukumaran 2014	?	?	?	+	+	+	+
Toneva 2012	?	+	?	+	+	+	+

High
 Unclear
 Low



Figure 5 – Frozen section: overview critical appraisal all included DTA studies* (1)

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Acikalın 2014	?	?	?	+	?	?	?
Bazot 2006	?	+	?	+	?	?	+
Bige 2011	?	+	?	+	+	+	+
Boriboonthirunsam 2004	?	+	?	+	?	+	+
Canis 2004	+	?	?	+	+	+	+
Cross 2012	+	+	?	+	+	+	+
Cuello 1999							
da Cunha Bastos 1983	?	?	?	+	?	?	?
Fanfani 2007	+	+	?	+	+	+	+
Garcia 1997	?	?	?	+	?	?	+
Geomini 2005	+	+	+	+	+	+	+
Gol 2003	?	?	+	?	?	?	+
Gorisek 2009	?	?	?	?	?	?	+
Hamed 1993	+	+	+	?	+	+	?
Ilker 2011	+	+	?	+	+	+	+
Ivan 2005	?	+	?	+	+	+	+
Kokka 2009	+	?	?	+	+	+	+
Lim 1997	?	+	?	+	+	+	+
Maheshwari 2006	?	?	?	+	?	?	+
Malipatil 2013	?	+	?	+	?	+	+
Naik 2006	+	?	?	+	+	+	+
Pavakis 2009	?	?	?	+	+	?	?
Pinto 2001	?	?	+	+	?	?	+
Puls 1997	+	?	+	+	?	+	?

*For three studies, critical appraisal is lacking due language or single critical appraisal only.



Figure 6 – Frozen section: overview critical appraisal all included DTA studies* (2)

Puls 1997	+	?	+	+	?	+	?
Rakhshan 2009	?	+	?	+	?	+	+
Rose 1994	?	?	?	+	?	?	+
Spann 1994							
Stewart 2006	+	+	+	+	+	+	+
Subbian 2013	?	+	?	?	+	+	+
Sukumaran 2014	?	?	?	+	+	+	+
Suprasert 2008	?	?	?	+	?	?	+
Tangjitgamol 2004	?	?	?	+	?	?	+
Taskiran 2008	+	?	?	+	+	?	+
Toneva 2012	?	+	?	+	+	+	+
Torres 1998							
Twaalfhoven 1991	?	?	?	?	?	?	+
Wakahara 2001	?	+	?	+	?	+	+
Wang 1998	?	+	+	+	+	+	+
Wasinghon 2008	+	?	?	+	+	+	+
Wootipoom 2006	?	?	?	+	?	?	+
Yarandi 2008	?	+	?	+	+	+	+
Yeo 1998	?	+	+	+	?	+	+

+

 High

?

 Unclear

+

 Low

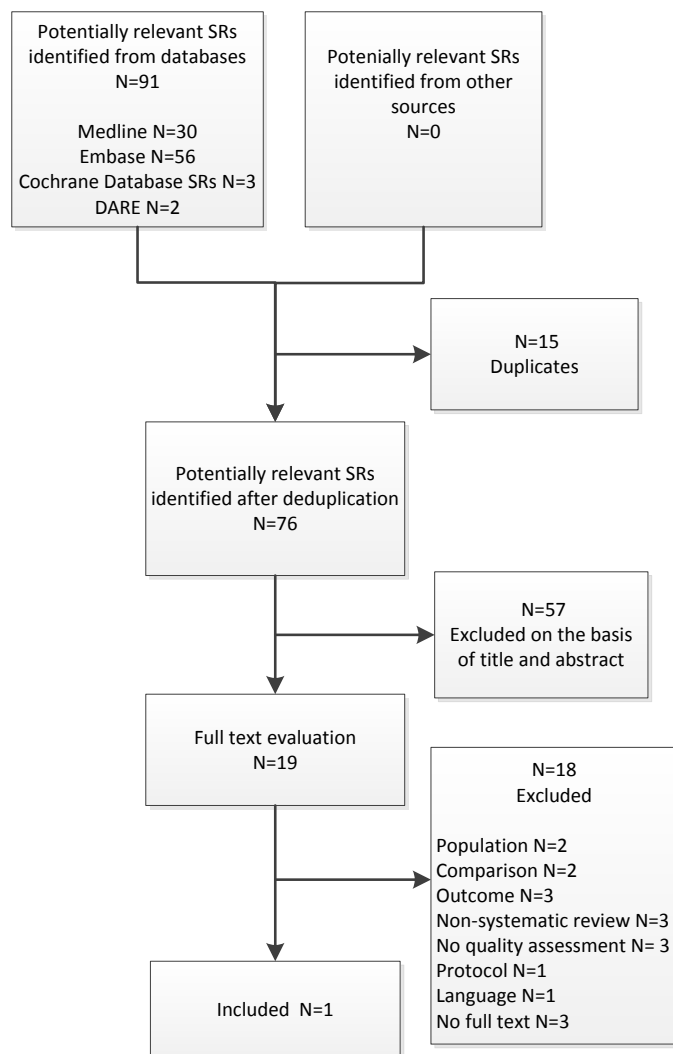


4.2.3. Lymphadenectomy

4.2.3.1. Selection of systematic reviews

On June 15, 2015 a search was performed to identify SRs regarding systematic pelvic and para-aortic lymphadenectomy in patients with borderline or (micro)invasive (presumed) early-stage ovarian cancer. MEDLINE, Embase, CDSR and DARE were searched from inception.

In total, 91 potentially relevant references were identified (Figure 7). After deduplication, 76 references remained. Based on title and abstract 57 references were excluded. Of the remaining nine references, one was included and eight were excluded with reason (Table 9).

**Figure 7 – PRISMA flowchart SRs lymphadenectomy**

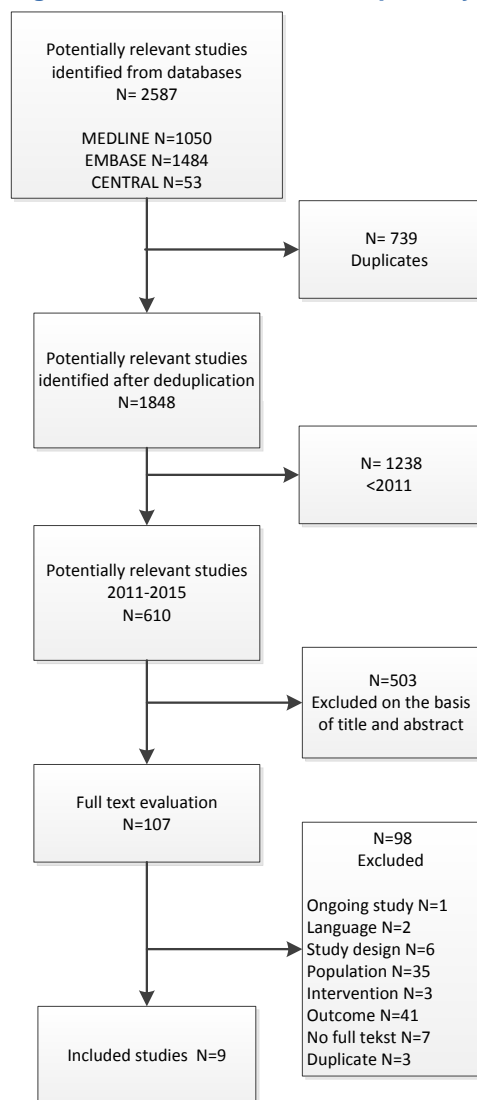
**Table 9 – Excluded SRs lymphadenectomy**

Reference	Reasons
Atienza-Amores 2014 ²⁹	Outcome
Bois 2009 ³⁰	No full text
Dodge 2012 ³¹	Outcome, one database searched and no methodological quality assessed in included studies
Faluyi 2009 ³²	Outcome
Gao 2015 ³³	Comparison
Gurumurthy 2014 ³⁴	Outcome
Hackethal 2008 ³⁵	Population
Haritwal 2004 ³⁶	One database searched, no methodological quality assessed in included studies
Kim 2010 ³⁷	Comparison
Kleppe 2014 ³⁸	Excluded on population
Kuhn 1991 ³⁹	No full text
Lecuru 1998 ⁴⁰	One database searched, no methodological quality assessed in included studies
Munstedt 2004 ⁴¹	Non-systematic review
Papadia 2004 ⁴²	Non-systematic review
Qin 2012 ⁴³	Language
Roy 1998 ⁴⁴	No full text
Shyamala 2010 ⁴⁵	Non-systematic review
Smits 2015 ⁴⁶	Protocol of systematic review

4.2.3.2. Selection of primary studies

On June 22, 2015 a search was performed to identify primary studies (any study design) that reported on prevalence of malignant disease in pelvic and para-aortic lymph nodes in patients with borderline or (micro)invasive (presumed) early-stage ovarian cancer undergoing systematic pelvic and para-aortic lymphadenectomy. MEDLINE, Embase and CENTRAL were searched from 2011 (search date of included systematic review).

In total, 2587 potentially relevant references were identified (Figure 8). After deduplication 1848 remained. Of those, 610 references published from 2011 to date were screened. Based on title and abstract 503 references were excluded. Of the remaining 107 references, after full-text screening, nine were included and 98 were excluded with reason (Table 10).

**Figure 8 – PRISMA flowchart primary studies lymphadenectomy**

**Table 10 – Excluded primary studies lymphadenectomy**

Reference	Reason
Akbayir 2012 ⁴⁷	Excluded on population
AlHilli 2013 ⁴⁸	Excluded on population
Aoki 2014 ⁴⁹	Excluded on study design
Ataseven 2014 ⁵⁰	Excluded on outcome
Azuar 2013 ⁵¹	Excluded on outcome
Bachmann2014 ⁵²	No full text available
Bae 2012 ⁵³	Excluded on outcome
Bennett 2015 ⁵⁴	Excluded on outcome
Berretta 2014 ⁵⁵	Excluded on population
Boren 2012 ⁵⁶	Excluded on population
Bostanci 2014 ⁵⁷	Excluded on language
Braicu 2013 ⁵⁸	Excluded on population
Brown 2014 ⁵⁹	Excluded on outcome
Capilna 2011 ⁶⁰	Excluded on population
Chang 2013 ⁶¹	Duplicate, included
Chang 2013 ⁶²	Excluded on population
Chatchotikawong 2015 ⁶³	Excluded on population
Chereau 2012 ⁶⁴	Excluded on study design
Cusido 2011 ⁶⁵	Excluded on population
Dell 2012 ⁶⁶	Excluded on intervention
Ditto 2014 ⁶⁷	Excluded on outcome
Eltabbakh 2011 ⁶⁸	No full text available
Ertas 2014 ⁶⁹	Excluded on population
Ertas 2014 ⁶⁹	Duplicate, excluded on population
Ertas 2014 ⁷⁰	Excluded on population



Reference	Reason
Euscher 2011 ⁷¹	Excluded on population
Gmyrek 2011 ⁷²	Excluded on outcome
Grabowski 2012 ⁷³	Excluded on outcome
Guvenal 2013 ⁷⁴	Excluded on outcome
Gyimadu 2012 ⁷⁵	Excluded on outcome
Haller 2011 ⁷⁶	Duplicate, included
Han 2012 ⁷⁷	Excluded on outcome
Hareyama 2012 ⁷⁸	Excluded on outcome
Hareyama 2015 ⁷⁹	Excluded on outcome
Hu 2013 ⁸⁰	Excluded on population
Ibeanu 2013 ⁸¹	Excluded on outcome
Kanat-Pektas 2011 ⁸²	Excluded on outcome
Karalok 2015 ⁸³	Excluded on population
Kiran 2015 ⁸⁴	Excluded on outcome
Lambaudie 2012 ⁸⁵	Excluded on population
Lazarou 2014 ⁸⁶	No full text available
Li 2014 ⁸⁷	Excluded on outcome
Magazzino 2011 ⁸⁸	Excluded on outcome
Mahdi 2011 ⁸⁹	Excluded on population
Mahdi 2011 ⁹⁰	Excluded on population
Mahdi 2013 ⁹¹	Excluded on outcome
Marpeau 2012 ⁹²	Excluded on study design
Matsuo 2012 ⁹³	Excluded on population
Matsuo 2014 ⁹⁴	Excluded on outcome
Matsuo 2014 ⁹⁵	Excluded on population
Matsuo 2015 ⁹⁶	Excluded on outcome



Reference	Reason
Mbarki 2011 ⁹⁷	Excluded on outcome
McNally 2015 ⁹⁸	Excluded on outcome
Meinhold-Heerlein 2014 ⁹⁹	Excluded on study design
Miyamoto 2011 ¹⁰⁰	Excluded on language
Miyamoto 2012 ¹⁰¹	Excluded on outcome
Momeni 2013 ¹⁰²	Excluded on population
Moore 2011 ¹⁰³	Excluded on population
Morales 2013 ¹⁰⁴	Excluded on intervention
Moreau-Claeys 2011 ¹⁰⁵	Excluded on population
Mury 2011 ¹⁰⁶	Excluded on outcome
Oh 2014 ¹⁰⁷	Excluded on population
Ohba 2012 ¹⁰⁸	Excluded on outcome
Ozalp 2014 ¹⁰⁹	No full text available
Pan 2011 ¹¹⁰	Excluded on population
Park 2011 ¹¹¹	Excluded on population
Park 2012 ¹¹²	Excluded on outcome
Park 2012 ¹¹³	Excluded on population
Paulsson 2013 ¹¹⁴	No full text available
Pereira 2013 ¹¹⁵	Excluded on population
Pereira 2014 ¹¹⁶	Excluded on outcome
Petry 2012 ¹¹⁷	Excluded on study design
Rauh-Hain 2013 ¹¹⁸	Excluded on outcome
Rauh-Hain 2013 ¹¹⁹	Excluded on outcome
Rauh-Hain 2015 ¹²⁰	Excluded on outcome
Rizzuto 2015 ¹²¹	Excluded on outcome
Romeo 2013 ¹²²	Excluded on population



Reference	Reason
Ruskin 2011 ¹²³	Excluded on outcome
Sato 2015 ¹²⁴	Ongoing study
Schnack 2014 ¹²⁵	Excluded on outcome
Schreuder 2012 ¹²⁶	Excluded on outcome
Shih 2011 ¹²⁷	Excluded on outcome
Shim 2013 ¹²⁸	Excluded on outcome
Signorelli 2013 ¹²⁹	Excluded on outcome
Signorelli 2014 ¹³⁰	Excluded on population
Song 2014 ¹³¹	Excluded on intervention
Sornsukolrat 2012 ¹³²	No full text available
Takano 2012 ¹³³	Excluded on study design
Terai 2013 ¹³⁴	Excluded on outcome
Thrall 2011 ¹³⁵	Excluded on population
Trillsch 2015 ¹³⁶	Excluded on outcome
Tsuboyama 2014 ¹³⁷	Excluded on outcome
Tsuda 2014 ¹³⁸	Excluded on population
Ulanday 2014 ¹³⁹	Excluded on population
Villet 2011 ¹⁴⁰	No full text available
Zanagnolo 2013 ¹⁴¹	Excluded on population
Zhao 2014 ¹⁴²	Excluded on population
Zikan 2015 ¹⁴³	Excluded on population

4.2.3.3. Critical appraisal

Systematic reviews

Of the one included review (Kleppe 2011¹⁴⁴), quality appraisal through the AMSTAR criteria was performed (Table 11). The review scored negatively on most of the items.

**Table 11 – Methodological quality systematic review (AMSTAR) lymphadenectomy**

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Kleppe 2011 ¹⁴⁴	-	?	+	-	-	-	-	-	NA	-	+

NA=not applicable

*less than 10 included studies

Quality appraisal of primary studies

All of the included primary studies are non-comparative observational studies. No validated tool for methodological quality assessment exists for this type of studies.

4.2.4. Adjuvant chemotherapy

To evaluate the benefits of adjuvant chemotherapy offered for borderline or invasive early-stage ovarian cancer, the searches of two Cochrane reviews^{32, 145} were updated on March 24th, 2015. The Cochrane Gynaecological Cancer Group searched the Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL; Issue 2, 2015), MEDLINE and EMBASE. All included RCTs of both reviews were checked whether they included a subgroup of patients with micro-invasive early-stage ovarian cancer. On April 8th, 2015 an additional search was performed in MEDLINE, EMBASE, Pubmed Central, and Cochrane central registry of studies to identify both randomized and non-randomized studies comparing the effectiveness of adnexectomy and surgical staging with adjuvant chemotherapy versus adnexectomy and surgical staging without adjuvant chemotherapy for patients with micro-invasive early-stage ovarian cancer.

Borderline ovarian tumours

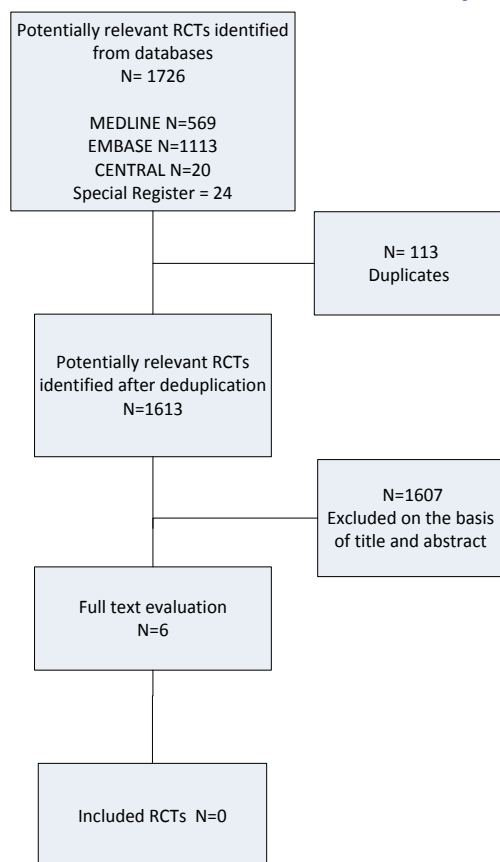
In total, 1726 potentially relevant references were identified for the update of Faluyi et al. (2010)³² (Figure 9). After deduplication 1613 remained. Based on title and abstract 1607 references were excluded. The remaining six references were excluded after full-text screening with reason (Table 12). No new RCTs were included for this research question.

Micro-invasive ovarian tumours

For this question, 1020 potentially relevant references were identified (Figure 10). After deduplication 882 remained. Based on title and abstract 872 references were excluded. The remaining ten references were excluded after full-text screening with reason (Table 13). No new RCTs or non-randomized studies were included for this research question.

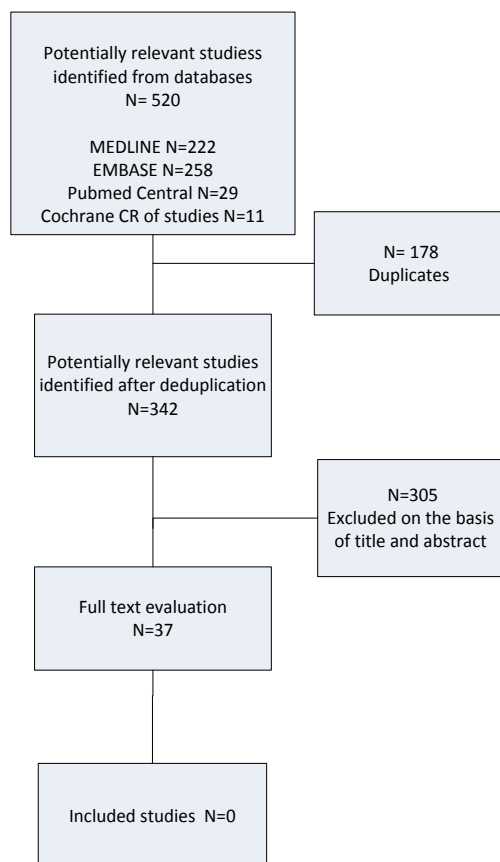
Invasive ovarian tumours

In total, 1020 potentially relevant references were identified for the update of Winter-Roach (2012)¹⁴⁵ from databases (Figure 11). After deduplication 882 remained. Based on title and abstract 872 references were excluded. Nine of the remaining ten references were excluded after full-text screening with reason (Table 14). One RCT was included for this research question.

**Figure 9 – PRISMA flowchart selection of RCTs adjuvant chemotherapy for borderline ovarian tumours**

**Table 12 – Excluded primary studies adjuvant chemotherapy for borderline ovarian tumours (n=6)**

Reference	Reason for exclusion
Joly F 2009 ¹⁴⁶	Excluded on population (early recurrent ovarian cancer)
Ledermann JA 2011 ¹⁴⁷	Excluded on population (relapsed ovarian cancer)
Mannel R 2011 ¹⁴⁸	Excluded on comparison (chemo vs. chemo)
Meier W 2009 ¹⁴⁹	Excluded on population (early recurrent ovarian cancer) Excluded on comparison (chemo vs. chemo)
Perren TJ 2011 ¹⁵⁰	Excluded on comparison (chemo vs. vascular endothelial growth factor inhibitor) Excluded on population (ovarian cancer)
Trimbos B. 2010 ¹⁵¹	Excluded on population (early ovarian cancer)

**Figure 10 – PRISMA flowchart selection of RCTs and non-randomized studies adjuvant chemotherapy micro-invasive ovarian tumours**

**Table 13 – Excluded RCTs and non-randomized studies adjuvant chemotherapy for micro-invasive disease (n=37)**

Reference	Reason for exclusion
Ceballos KM 2006 ¹⁵²	Excluded on intervention
Cusido M 1999 ¹⁵³	Excluded on language
Damak T 2014 ¹⁵⁴	Excluded on population
Dgani R 1990 ¹⁵⁵	Excluded on population
Du Bois A 2013 ¹⁵⁶	Excluded on design
Eltabbakh GH 2000 ¹⁵⁷	Excluded on design
Gilks CB 2003 ¹⁵⁸	Excluded on design
Haritwal A 2014 ³⁶	Excluded on design
Hogberg T 2001 ¹⁵⁹	Excluded on design
Kaern J 1993a ¹⁶⁰	Excluded on population
Kaern J 1993b ¹⁶¹	Excluded on population
Kane A 2009 ¹⁶²	Excluded on design
Kennedy AW 1996 ¹⁶³	Excluded on comparison
Laurent I 2008 ¹⁶⁴	Excluded on intervention
Leary A 2014 ¹⁶⁵	Excluded on population
Leiserowitz G 2005 ¹⁶⁶	Excluded on design
Leitao MM 2004 ¹⁶⁷	Excluded on population
Leitao MM 2011 ¹⁶⁸	Excluded on design
Li Y 2003 ¹⁶⁹	Excluded on language
Li ZX 1994 ¹⁷⁰	Excluded on language
Linasma V 1990 ¹⁷¹	No PDF available
Manchul LA 1992 ¹⁷²	No PDF available
Massad LS 1991 ¹⁷³	Excluded on population
Morice P 2001 ¹⁷⁴	No PDF available
Park JY 2011 ¹¹¹	Excluded on population
Raymond E 1997 ¹⁷⁵	Excluded on population



Reference	Reason for exclusion
Rettenmaier MA 2010 ¹⁷⁶	Excluded on population
Shih KK 2010 ¹⁷⁷	Excluded on population
Shih KK 2011 ¹²⁷	Excluded on design
Trimble CL 2002 ¹⁷⁸	Excluded on population
Tulpin L 2008 ¹⁷⁹	No PDF available
Uzan C 2011 ¹⁸⁰	Excluded on population
Vasconcelos I 2015a ¹⁸¹	Excluded on population
Vasconcelos I 2015b ¹⁸²	Excluded on design
Vergote IB 1992 ¹⁸³	Excluded on comparison
Yokoyama Y 2006 ¹⁸⁴	Excluded on population
Zhang Z 1998 ¹⁸⁵	Excluded on language

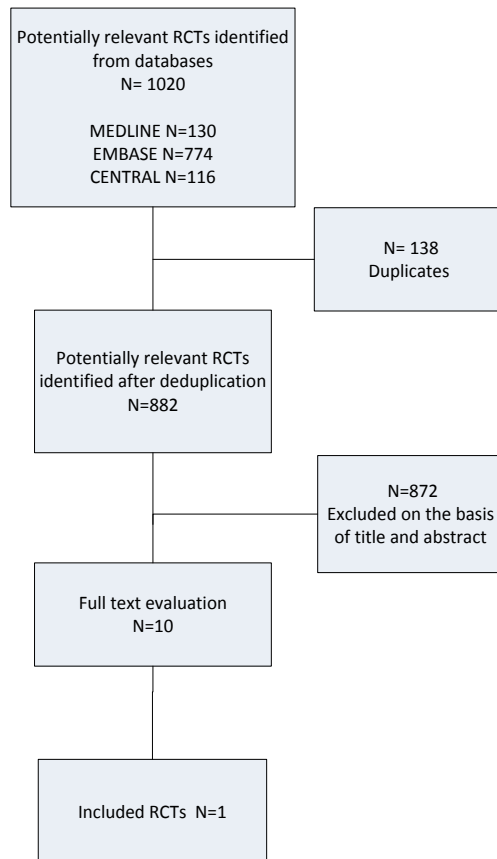
**Figure 11 – PRISMA flowchart selection of RCTs adjuvant chemotherapy for invasive early stage ovarian cancer**


Table 14 – Excluded RCTs adjuvant chemotherapy for invasive early stage ovarian cancer

Reference	Reason for exclusion
Bapsy PP 2012 ¹⁸⁶	No PDF available
Bookman MA 2011 ¹⁸⁷	Excluded on design
Burger RA 2012 ¹⁸⁸	Excluded on design
Cascales PA 2011 ¹⁸⁹	Excluded on design
Cliby W 2013 ¹⁹⁰	Excluded on design
Cui S 2012 ¹⁹¹	Excluded on design
Fujiwara K 2012 ¹⁹²	Excluded on design
Geurts SM 2011 ¹⁹³	Excluded on design
Gruenigen VE 2012 ¹⁹⁴	Excluded on population

Critical appraisal of selected systematic reviews

The results of the risk of bias assessment (using the AMSTAR checklist) for the two included Cochrane systematic reviews are presented in Table 15. All items scored low risk of bias (high methodological quality).

Risk of bias for the included RCT regarding research question 5c¹⁹⁵ had been assessed by Winter-Roach et al., as earlier publications of this RCT were already included in their systematic review.¹⁴⁵

Table 15 – Methodological quality of the included systematic reviews (AMSTAR) regarding adjuvant chemotherapy in patients with borderline or (micro-) invasive early-stage ovarian cancer

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Faluyi 2010 ³²	+	+	+	+	+	+	+	+	N/A	N/A*	+
Winter Roach 2012 ¹⁴⁵	+	+	+	+	+	+	+	+	+	N/A*	+

NA=not applicable

*less than 10 included studies

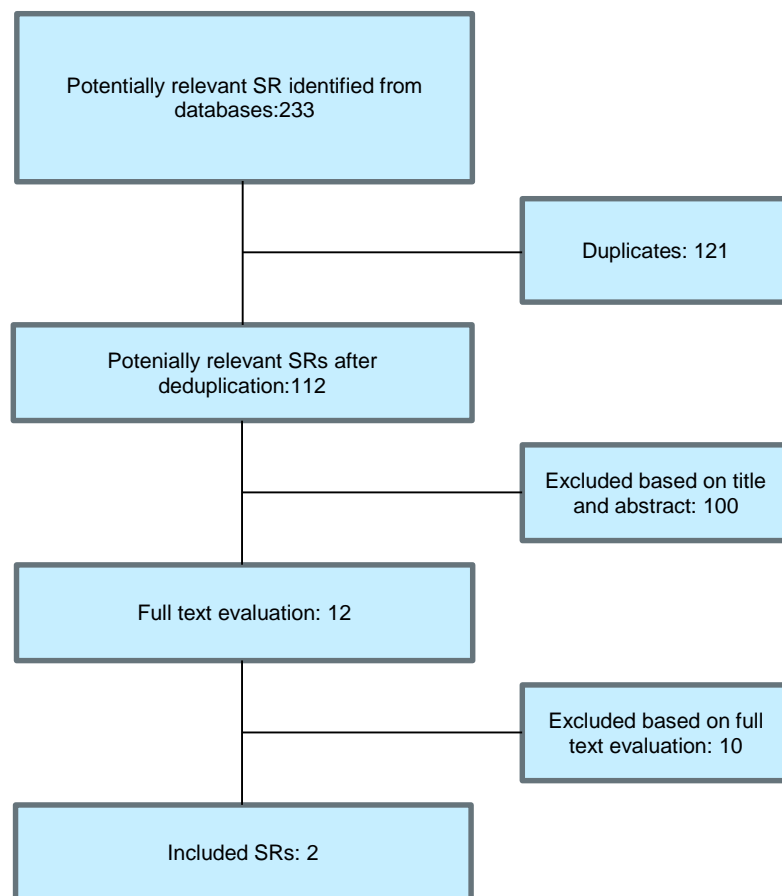


4.2.5. Laparoscopic surgery

Selection of systematic reviews

On March 09, 2015 a search was performed to identify SRs evaluating laparoscopic surgery for presumed early stage ovarian cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched.

In total 233 potential relevant references were identified (Figure 12). After de-duplication, 112 unique references remained. Based on title and abstract 100 reviews were excluded. Twelve reviews were included for full-text evaluation. Of these, eight were excluded with reasons (Table 16). Two further reviews were excluded based on critical appraisal (Table 17).^{196, 197}

**Figure 12 – Study flow of selection of SRs**

**Table 16 – Excluded SRs based on full-text evaluation**

Reference	Reason for exclusion
Lu 2015¹⁹⁸	Included
Matsushita 2014¹⁹⁹	Case-series, no comparison group
Lu 2014²⁰⁰	abstract
Bogani 2014¹⁹⁷	Included
Park 2013¹⁹⁶	Included
Mandic 2013²⁰¹	Narrative review
Lu 2013²⁰²	Full text not available
Lawrie 2013²⁰³	Included
Brockbank 2013²⁰⁴	No comparison with laparotomy
Dodge 2012³¹	Guideline, insufficient reporting of the systematic review
Covens 2012²⁵	Medline search only, from 2004 to 2009
Leblanc 2006²⁰⁵	Narrative review, no report of systematic search

Quality appraisal of selected systematic reviews

Table 17 shows the results of the risk of bias assessment for the included systematic review, using AMSTAR criteria.


Table 17 – Methodological quality of the included systematic review (AMSTAR)

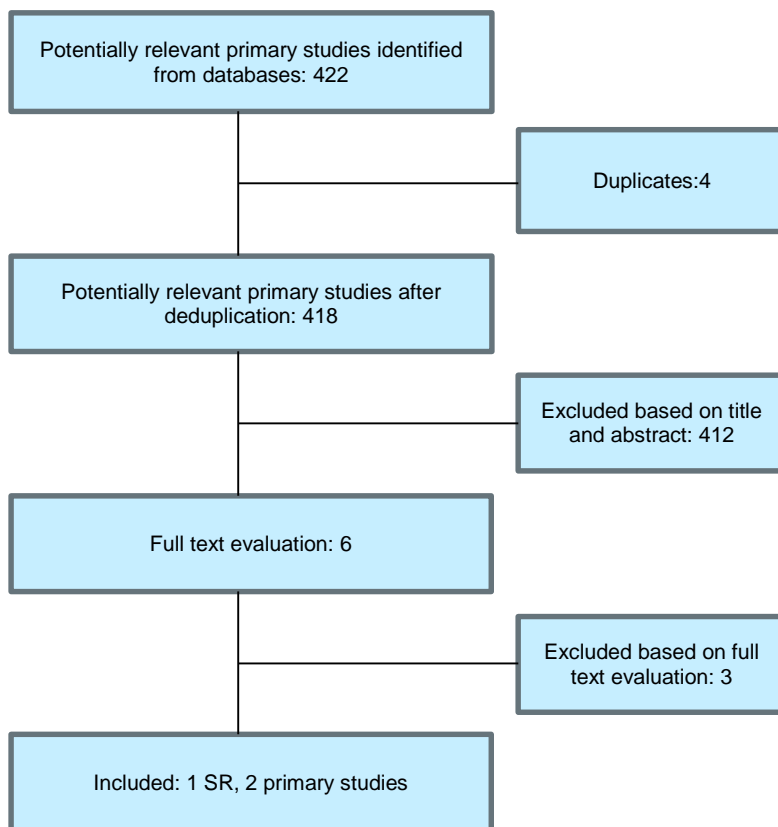
Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Lu 2015 ¹⁹⁸	Y	Y	Y	?	N	Y	Y	Y	N	Y	N
Lawrie 2013 ²⁰³	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	Y
Park 2013 ¹⁹⁶	Y	Y	Y	N	N	Y	N	N	N	Y	N
Bogani 2014 ¹⁹⁷	?	?	Y	N	N	Y	N	N	N	N	N
Zhang 2015 ²⁰⁶	Y	Y	Y	Y	N	Y	N	N	N	N	N

Selection of primary studies

On October 12, 2015 a search was performed to identify RCTs and non-randomized comparative studies evaluating laparoscopic surgery for presumed early stage ovarian cancer. The search date of Lu 2015¹⁹⁸ was used as starting point. MEDLINE (including PreMedline), Embase and CENTRAL were searched, limited from 2013 onwards. In total, 422 potential relevant references were identified (Figure 13). After de-duplication, 418 unique references remained. Based on title and abstract 412 studies were excluded.

After full text evaluation (Table 18), three papers were included, one systematic review with search date May 2014²⁰⁶ and two primary non-randomized studies.^{207, 208} The two primary studies were already included in the systematic review of Zhang et al (Table 17). A third study that was included in the review of Zhang et al., but not in the review of Lu et al. was excluded as patients who were treated with laparoscopy converted to laparotomy were analysed separately and not all patients underwent comprehensive staging.²⁰⁹

Both newly included primary studies were non-randomized studies with a high risk of bias as no case-mix adjustment was performed.

**Figure 13 – Study flow of selection of primary studies**

**Table 18 – Laparoscopic surgery early-stage ovarian cancer: excluded studies based on full text evaluation**

Reference	Reason for exclusion
Zhang Y. 2015²⁰⁶	Systematic review, included
Zhang Z.-M. 2014²¹⁰	Chinese
Liu 2014²⁰⁸	Included in Zhang et al. 2015
Koo 2014²⁰⁷	Included in Zhang et al. 2015
Gallotta 2014²¹¹	No comparator group with laparotomy
Aoki 2014²¹²	Opinion paper, narrative

4.2.6. Laparoscopy, PET-CT and MRI to predict end result of cytoreductive surgery

4.2.6.1. Systematic reviews

On January 22, 2015 a search was performed to identify SRs regarding PET-CT, laparoscopy and (diffusion) MRI to predict complete/optimal resection of advanced stage disease in patients with advanced stage ovarian cancer considered eligible for debulking surgery based on CT-scan. MEDLINE, Embase, CDSR and DARE were searched from inception.

In total, 233 potentially relevant references were identified (Figure 14). After deduplication, 168 references remained. Based on title and abstract 159 references were excluded. Of the remaining nine references, one was included²¹³ and eight were excluded with reason (Table 19).

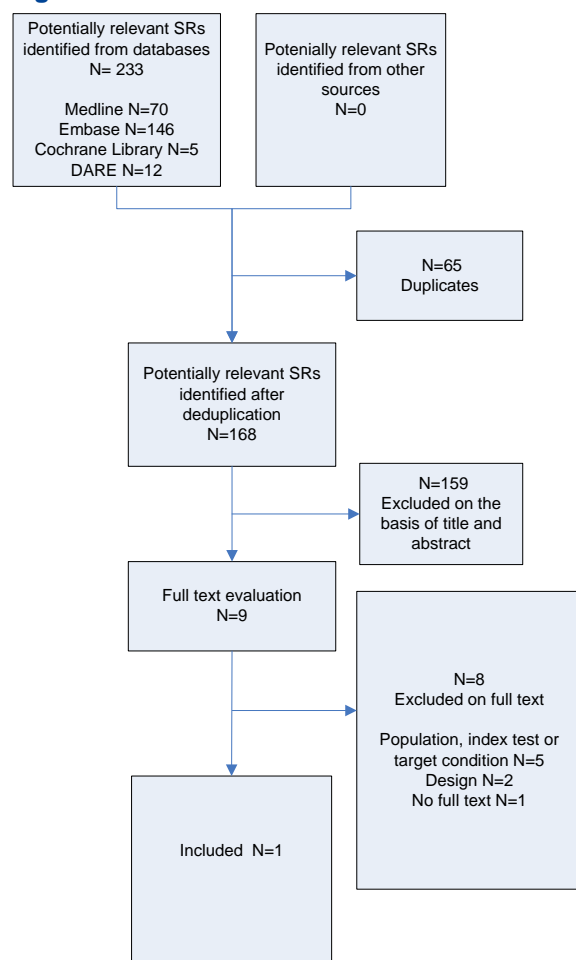
**Figure 14 – PRISMA flowchart selection of SRs prediction end result of surgery**


Table 19 – Prediction of end result of cytoreductive surgery: excluded SRs based on full-text evaluation

Reference	Reasons
Bertagna 2013 ²¹⁴	Index test and population not of interest
Chang 2013 ²¹⁵	Target condition not of interest
Havrilesky 2005 ²¹⁶	Target condition not of interest
Hoh 1998 ²¹⁷	No PDF
Ibeanu 2010 ²¹⁸	No systematic review
Lai 2014 ²¹⁹	Unclear index test and population
Musto 2011 ²²⁰	No SR
Yuan 2012 ²²¹	Target condition not of interest; mixed population

Quality appraisal of selected systematic reviews

Of the one included review (Rutten 2014),²¹³ quality appraisal through the AMSTAR criteria was performed. The review scored positively on the majority of the items. However, the SR failed to address whether there was a conflict of interest for both the review and the included studies. Overall, the SR is considered as having a 'low risk' of bias (Table 20).

Table 20 – Prediction end result of surgery: critical appraisal of included SR

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of included and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Rutten 2014 ²¹³	+	+	+	+	+	+	+	+	+	NA*	-

NA=not applicable

*less than 10 included studies

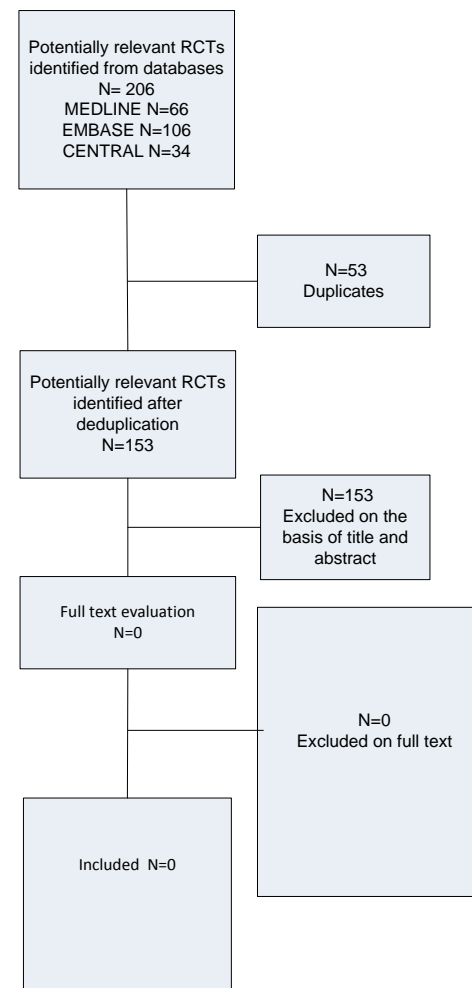


4.2.6.2. Randomized controlled trials

On February 16, 2015 a search was performed to identify RCTs regarding the effect on patient important outcomes of using PET-CT, laparoscopy or (diffusion) MRI to predict complete/optimal resection of advanced stage disease in patients with advanced stage ovarian cancer considered eligible for debulking surgery based on CT-scan. MEDLINE, Embase and CENTRAL were searched from inception.

In total, 206 potentially relevant references were identified (Figure 15). After deduplication 153 references remained. Based on title and abstract all references were excluded.

Figure 15 – PRISMA flowchart selection of RCTs prediction end result of surgery



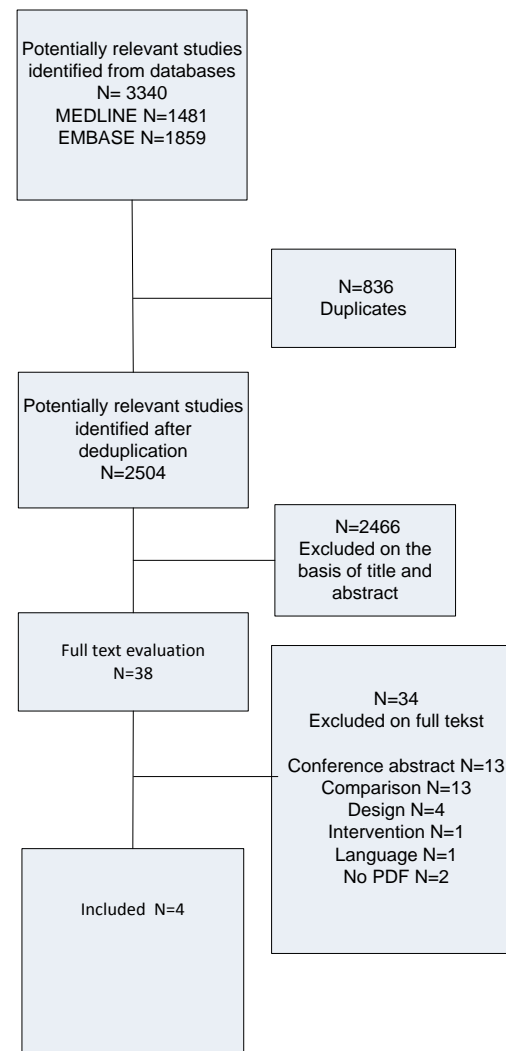


4.2.6.3. Diagnostic accuracy studies

On February 17, 2015 a search was performed to identify diagnostic test accuracy studies regarding PET-CT, laparoscopy or (diffusion) MRI to predict complete/optimal resection of advanced stage disease in patients with advanced stage ovarian cancer considered eligible for debulking surgery based on CT-scan. MEDLINE and Embase were searched from inception.

In total, 3340 potentially relevant references were identified (Figure 16). After deduplication, 2504 references remained. Based on title and abstract 2466 references were excluded. Of the remaining 38 references, four were included²²²⁻²²⁵ and 34 were excluded with reason (Table 21).

Figure 16 – PRISMA flowchart selection of DTA prediction end result of surgery



**Table 21 – Prediction of end result of surgery: excluded DTA studies based on full text selection**

Reference	Reasons
Alessi 2014 ²²⁶	Conference abstract
Baiocchi 2011 ²²⁷	Conference abstract
Bats 2011 ²²⁸	Conference abstract
Bats 2012 ²²⁹	Comparison not of interest
Buist 1994 ²³⁰	Comparison not of interest
Capo Pons 2013 ²³¹	Conference abstract
Caresia Aroztegui 2013 ²³²	Conference abstract
Castellucci 2007 ²³³	Comparison not of interest
Chung 2013 ²³⁴	Conference abstract
De Iaco 2010 ²³⁵	Conference abstract
De Iaco 2011 ²³⁶	Comparison not of interest
Drieskens 2003 ²³⁷	Comparison not of interest
Fruscio 2013 ²³⁸	Comparison not of interest
Funicelli 2010 ²³⁹	Comparison not of interest
Hynninen 2012a ²⁴⁰	Comparison not of interest
Hynninen 2012b ²⁴¹	Conference abstract
Hynninen 2013 ²⁴²	Comparison not of interest
Intriago 2011 ²⁴³	Conference abstract
Kim 2013 ²⁴⁴	Comparison not of interest
Kitajima 2008 ²⁴⁵	Comparison not of interest
Kubik-Huch 2000 ²⁴⁶	Comparison not of interest
Kurtz 1999 ²⁴⁷	Index test not of interest
Martinelli 2014 ²⁴⁸	Conference abstract
Michielsen 2012 ²⁴⁹	Conference abstract
Michielsen 2014 ²⁵⁰	Comparison not of interest
Mousavi 2010 ²⁵¹	No DTA study



Reference	Reasons
Risum 2008 ²⁵²	DTA data could not be retrieved
Risum 2011 ²⁵³	No DTA study
Semelka 1993 ²⁵⁴	Comparison not of interest
Shim 2013a ²⁵⁵	Conference abstract
Shim 2013b ²⁵⁵	Conference abstract
Stark 2010 ²⁵⁶	No DTA study
Torpy 2011 ²⁵⁷	No DTA study
Zhu 1999 ²⁵⁸	Language (Chinese)

Quality appraisal of selected DTA studies

Three of the four included studies had high risk of bias (due to patient selection and no blinded assessment of the reference test, amongst others). All studies had applicability concerns (spectrum of patients not applicable; index test not used as add-on test in women in whom CT indicates a resectable tumour; threshold for resectability undefined) (Figure 17).



Figure 17 – Summary of the QUADAS assessments of included DTA studies

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Espada 2013	–	–	–	+	–	–	+
Forstner 1995	+	+	?	+	–	–	?
Qayyum 2005	–	+	–	+	–	–	–
Shim 2015	–	+	–	+	+	–	–

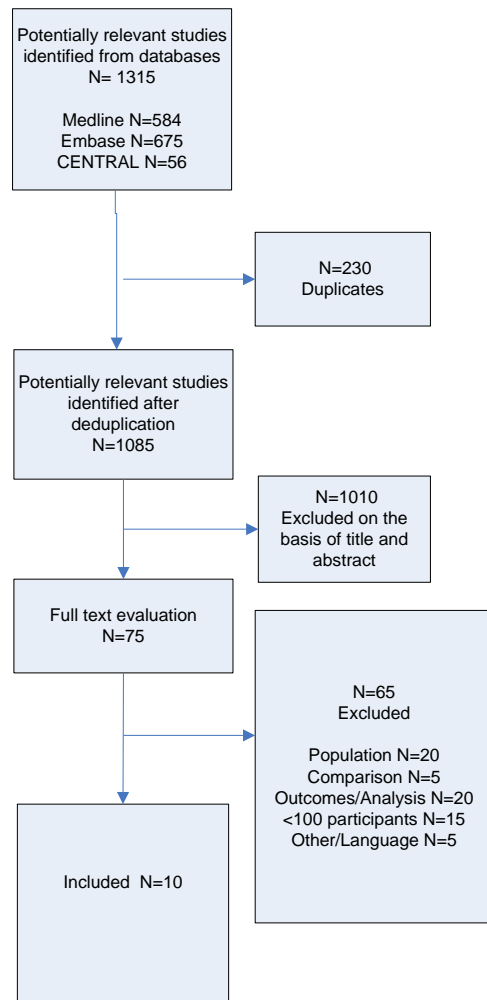
High
 Unclear
 Low



4.2.7.1. Prognostic value end result of surgery

Table 22 – Prognostic value end result of surgery: quality appraisal of the included SR

[illegible]

**Figure 18 – Prognostic value end result of surgery: study flow of selection of primary studies**

**Table 23 – Prognostic value end result of surgery: excluded studies based on full text selection**

Reference	Reasons
Abaid 2011 ²⁷⁰	<100 participants
Altman 2012 ²⁷¹	also included patients undergoing IDS; not analysed separately
Bacic 2013 ²⁷²	<100 participants
Bakrin 2013 ²⁷³	<100 participants
Barlin 2012 ²⁷⁴	no multivariate analysis
Barlin 2013 ²⁷⁵	only debulking status 0.1-1.0 cm
Barriuso 2010 ²⁷⁶	<100 participants
Bats 2012 ²²⁹	<100 participants
Bengrine-Lefevre 2011 ²⁷⁷	also included patients undergoing IDS; not analysed separately
Bereder 2009 ²⁷⁸	included also recurrent cancer
Braicu 2011 ²⁷⁹	no results according to debulking status
Burger 2013 ²⁸⁰	no results according to debulking status
Chao 2013 ²⁸¹	<100 participants
Chereau 2011 ²⁸²	<100 participants
Chi 2010 ²⁸³	no results according to debulking status
Chi 2012 ²⁸⁴	no multivariate analysis`
Chua 2011 ²⁸⁵	majority not ovarian cancer
David 2013 ²⁸⁶	<100 participants
du Bois 2010 ²⁸⁷	also stage <IIIC included
Fanfani 2012 ²⁸⁸	also included patients undergoing IDS; not analysed separately
Fu 2014 ²⁸⁹	also stage <III included
Gerestein 2011 ²⁹⁰	predictors of suboptimal debulking
Gonzalez 2013 ²⁹¹	no results according to debulking status / Spanish
Green 2006 ²⁹²	only debulking status >1 cm
Greimel 2013 ²⁹³	no results according to debulking status
Hoskins 2010 ²⁹⁴	also stage <IIIC included and patients undergoing IDS



Reference	Reasons
Hosono 2011 ²⁹⁵	only debulking status >1 cm
Hyman 2012 ²⁹⁶	no results according to debulking status
Kairbayev 2013 ²⁹⁷	<100 participants
Kang 2011 ²⁹⁸	no multivariate analysis; outcomes not of interest; NAC included
Kolev 2010 ²⁹⁹	no results according to debulking status
Konigsrainer 2012 ³⁰⁰	only 33 ovarian cancer cases; not analysed separately; no debulking results
Landrum 2013 ³⁰¹	RD <0.5 and 0.5-1.0 vs microscopic (and not 1.0 cm)
Luyckx 2012 ³⁰²	also included patients undergoing IDS; not analysed separately
Mackay 2010 ³⁰³	no results according to debulking status
Mahner 2013³⁰⁴	also stage II included
Martinez 2011³⁰⁵	<100 participants
Moslemi-Kebria 2012³⁰⁶	no results according to debulking status
Mury 2011¹⁰⁶	no results according to debulking status
Oe 2011³⁰⁷	<100 participants
Perri 2013³⁰⁸	also included patients with NAC; not analysed separately
Phippen 2013³⁰⁹	<100 participants
Rauh-Hain 2012a³¹⁰	also included patients with NAC; not analysed separately
Rauh-Hain 2012b³¹¹	also included patients with uterine cancer
Riester 2014³¹²	gene predictors + MA
Risum 2012³¹³	looks at role of PET for selecting patients for NAC
Rutten 2014³¹⁴	outcome not of interest (DSS)
Sabbatini 2013³¹⁵	no results according to debulking status / comparison
Sayyah-Melli 2013³¹⁶	<100 participants
Sehouli 2010³¹⁷	also included patients undergoing IDS; not analysed separately
Seidman 2012³¹⁸	no multivariate analysis
Storr 2012 ³¹⁹	also stage <III included



Reference	Reasons
Tang 2008 ³²⁰	<100 participants
Taskin 2013 ³²¹	no results according to debulking status (nor in PDS arm)
Teo 2013 ³²²	mixed population (only 39 with ovarian cancer)
Terauchi 2011 ³²³	Japanese
Tiuliandin 2011 ³²⁴	included also recurrent cancer
Trope 2012 ³²⁵	RD 0.1-2.0 and >2.0 vs microscopic (and not 1.0 cm)
Tsolakidis 2011 ³²⁶	<100 participants
van Altena 2012 ³²⁷	also stage <IIIC included
Van De Laar 2014 ³²⁸	included also recurrent cancer / secondary debulking
van Meurs 2013 ³²⁹	predictors of benefit from NACT; no survival data according to debulking status
Vergote 2010 ³³⁰	no multivariate analysis (see suppl materials page 24)
Walters 2013 ³³¹	outcomes not of interest
Zapardiel 2011 ³³²	no multivariate analysis according to debulking status

The risk of bias assessments of the ten included comparative observational studies and the eleven studies that were already included in Elattar's review are summarised in Figure 19. All studies scored high risk for selection bias. In all studies blinding was not reported. Blinding of personnel and patients for the debulking results, however, is not possible and blinding of the outcome assessors is not relevant for objective outcomes. All studies but two studies scored low risk of bias for completeness of follow-up (which may be due to the selection process: only patients with complete follow-up might have been selected). The risk of selective reporting was not clear in all studies. Only two studies scored low risk of other bias and seven scored high risk, due to adjusted HRs coming from prognostic models. No details were presented on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Eight studies scored low risk of bias for representative sample and 11 studies high risk bias (because the population did not comprise of women with stage IIIC/IV).


Figure 19 – Prognostic value end result of surgery: risk of bias assessment of observational studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Representative sample
Akahira 2001	?	?	+	?	?	?	?
Aletti 2006	?	?	+	?	?	?	?
Bristow 2011	?	?	+	?	?	?	?
Chan 2003	?	?	?	?	?	?	+
Chang 2012a	?	?	+	?	?	?	+
Chang 2012b	?	?	+	?	?	?	?
Chi 2001	?	?	+	?	?	?	+
Chi 2006	?	?	+	?	?	?	?
Eisenkop 2003	?	?	+	?	?	?	?
Hofstetter 2013	?	?	+	?	?	?	+
Langstraat 2011	?	?	+	?	?	?	?
McGuire 1995	?	?	+	?	?	?	+
Peiretti 2010	?	?	+	?	?	?	+
Peiretti 2012	?	?	+	?	?	?	?
Polteraue 2012	?	?	+	?	?	?	?
Rodriguez 2013	?	?	+	?	?	?	+
Salani 2007	?	?	?	?	?	?	?
Van Geene 1996	?	?	+	?	?	?	+
Wimberger 2010	?	?	+	?	?	?	?
Winter 2007	?	?	+	?	?	?	?
Winter 2008	?	?	+	?	?	?	?



4.2.7.2. Effect of ultra-radical surgery

The starting point was a high-quality Cochrane systematic review (Table 24).³³³ On January 16, 2015 a search was performed in MEDLINE, Embase and CENTRAL to identify RCTs and comparative observational studies regarding the effectiveness of ultra-radical (extensive) surgery in patients with stage IIIc-IV ovarian cancer. In total, 2,381 potentially relevant references were identified (Figure 20). After deduplication, 2,043 references remained. Based on title and abstract 1,985 references were excluded. Of the remaining 58 references, two were included^{261, 302} and 56 were excluded with reason (Table 25).

Table 24 – Effect of (ultra)radical surgery: quality appraisal of the included SR

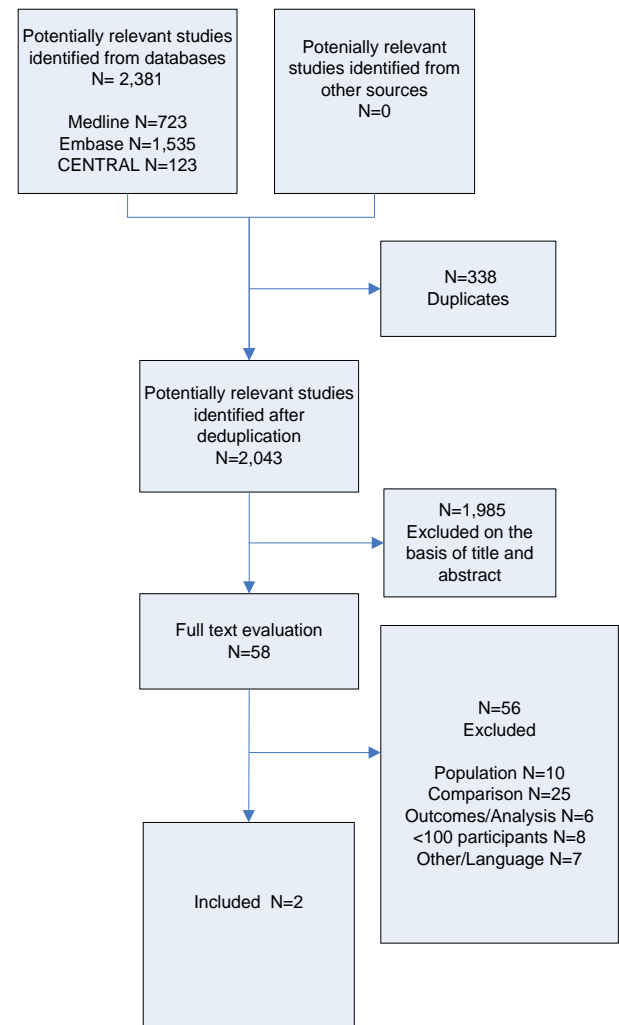
Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Ang 2011 ³³³	+	+	+	+	+	+	+	+	NA	NA*	+

NA=not applicable

*less than 10 included studies



Figure 20 – PRISMA flowchart selection effect of (ultra)radical surgery



**Table 25 – Effect of (ultra)radical surgery: excluded studies based on full text selection**

Reference	Reasons
Angioli 2013 ³³⁴	<100 participants
Barlin 2013 ²⁷⁵	no multivariate analysis
Butler 2012 ³³⁵	<100 participants; conference abstract
Cascales 2014 ³³⁶	intervention HIPEC
Chang 2012 ²⁶²	no ultra-radical surgery
Chereau 2011 ³³⁷	mixed FIGO stages; no multivariate analysis
Chua 2011 ²⁸⁵	comparison not of interest
Clark 2012 ³³⁸	outcomes not of interest; conference abstract
Clark 2014 ³³⁹	comparison not of interest
Cormier 2012 ³⁴⁰	no ultra-radical surgery; conference abstract
Favero 2014 ³⁴¹	comparison not of interest / conference abstract
Ferrero 2014 ³⁴²	comparison not of interest
Fotopoulou 2012 ³⁴³	comparison not of interest; conference abstract
Fotopoulou 2013 ³⁴⁴	no comparator
Gremeau 2014 ³⁴⁵	comparison not of interest
Guyon 2014 ³⁴⁶	comparison not of interest
Hamilton 2011 ³⁴⁷	comparison not of interest
Hudry 2013 ³⁴⁸	comparison not of interest
Hwang 2014 ³⁴⁹	mixed population; comparison not of interest
Janda 2014 ³⁵⁰	comparison not of interest
Jiang 2013 ³⁵¹	included, but conference abstract
Kato 2013a ³⁵²	population not of interest
Kato 2013b ³⁵³	comparison not of interest
Kehoe 2013 ³⁵⁴	comparison not of interest
Kim 2011 ³⁵⁵	comparison not of interest; <100 participants
Kolev 2014 ³⁵⁶	recurrent cancer



Reference	Reasons
Kristensen 2014 ³⁵⁷	borderline tumours
Li 2014 ⁸⁷	comparison not of interest
Liu 2013a ³⁵⁸	germ cell tumours; article in Chinese
Liu 2013b ³⁵⁹	germ cell tumours; <100 participants
Martinez 2014 ³⁶⁰	conference abstract
McCann 2011 ³⁶¹	no multivariate analysis
Oshita 2013 ³⁶²	includes only stages pT1-2
Park 2011 ³⁶³	no ultra-radical surgery; conference abstract
Pathiraja 2011 ³⁶⁴	<100 participants; conference abstract
Pathiraja 2013 ³⁶⁵	<100 participants; outcomes not of interest
Perri 2013 ³⁰⁸	comparison not of interest
Pushpalatha 2011 ³⁶⁶	comparison not of interest
Qin 2012 ⁴³	meta-analysis; comparison not of interest
Ratnavelu 2014 ³⁶⁷	<100 participants; conference abstract
Rodriguez 2012 ³⁶⁸	conference abstract
Rodriguez 2013 ²⁶⁸	patients with suboptimal debulking were excluded
Rouzier 2010 ³⁶⁹	mixed population; comparison not of interest
Sakai 2012 ³⁷⁰	no ultra-radical surgery
Sandadi 2013 ³⁷¹	comparison not of interest
Scalici 2014 ³⁷²	comparison not of interest
Szczesny 2014 ³⁷³	conference abstract
Sehouli 2010 ³¹⁷	comparison not of interest
Stefanovic 2011 ³⁷⁴	<100 participants
Sundar 2014 ³⁷⁵	<100 participants; conference abstract
van de Laar 2014 ³⁷⁶	protocol for a new study; applies to recurrent cancer
Wat 2012 ³⁷⁷	<100 participants; conference abstract



Reference	Reasons
Wright 2012 ³⁷⁸	outcomes not of interest
Yildirim 2014 ³⁷⁹	no comparator
Zamurovic 2013 ³⁸⁰	no multivariate analysis
Zapardiel 2012 ³⁸¹	no multivariate analysis

Quality appraisal of included observational studies is summarized in Table 21. All studies scored high risk of bias for selection and other bias, which was based on the adjusted HRs coming from prognostic models. No details were presented on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance).

Figure 21 – Effect of (ultra)radical surgery: risk of bias assessment of observational studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Details of assignment of patients reported?	Representative ultra-radical surgery group?	Representative standard surgery group?	Comparability of groups?
Aletti 2006	+	+	?	+	+	+	+	?	?	+
Chang 2012	+	+	?	+	?	+	+	?	?	?
Luyckx 2012	+	+	?	+	?	+	?	?	?	?



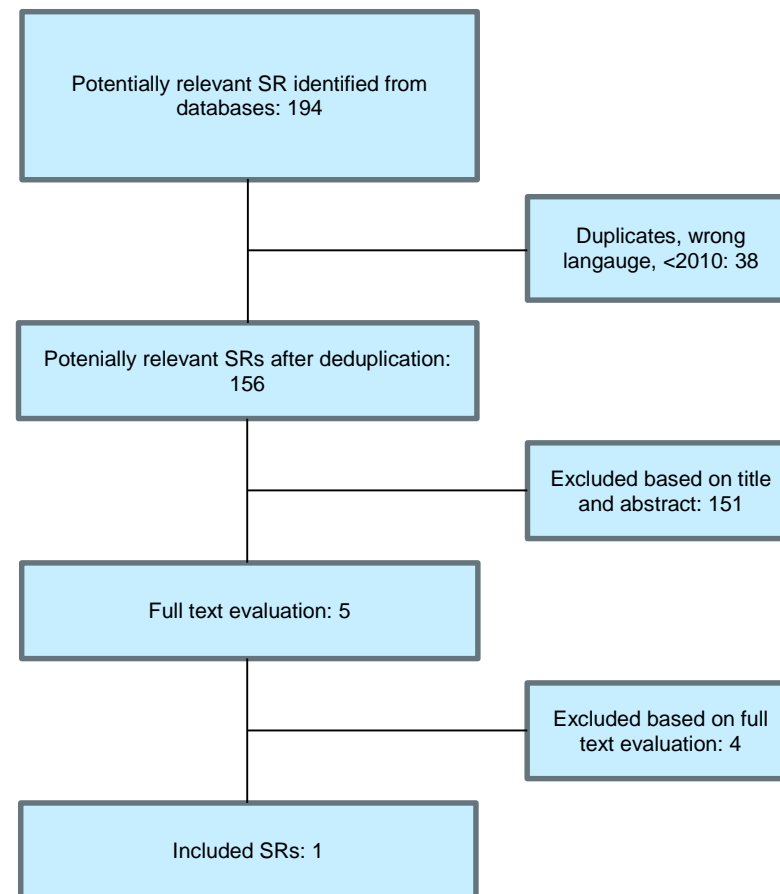
4.2.8. *Neo-adjuvant chemotherapy and interval debulking versus upfront surgery*

4.2.8.1. *Systematic reviews*

On January 13, 2015 a search was performed to identify SRs comparing neoadjuvant chemotherapy and interval debulking versus upfront debulking followed by chemotherapy in women with advanced ovarian cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched.

In total 194 potential relevant references were identified (Figure 22). After de-duplication and removal of references in the wrong language or published before 2010, 156 unique references remained. Based on title and abstract 151 reviews were excluded. Five reviews were included for full-text evaluation. Of these, four were excluded with reasons (Table 26) and one was included.³⁸²

Figure 22 – Study flow of selection of SRs



**Table 26 – Excluded SRs based on full-text evaluation**

Reference	Reason for exclusion
Dai-yuan M, Bang-xian T, Xian-fu L, Ye-qin Z, Hong-Wei C. A meta-analysis: neoadjuvant chemotherapy versus primary surgery in ovarian carcinoma FIGO stageIII and IV. World Journal of Surgical Oncology. 2013;11(267)	One of the included RCTs evaluated irrelevant comparison
Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database Syst Rev. 2010(10):CD006014	Updated by Tangjitgamol S 2013
Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews. 2013;4	Wrong comparison
Vitale SG, Marilli I, Lodato M, Tropea A, Cianci A. The role of cytoreductive surgery in advanced-stage ovarian cancer: a systematic review. Updates Surg. 2013;65(4):265-70	Narrative review

Quality appraisal of selected systematic reviews

Table 27 shows the results of the risk of bias assessment for the included systematic review, using AMSTAR criteria.

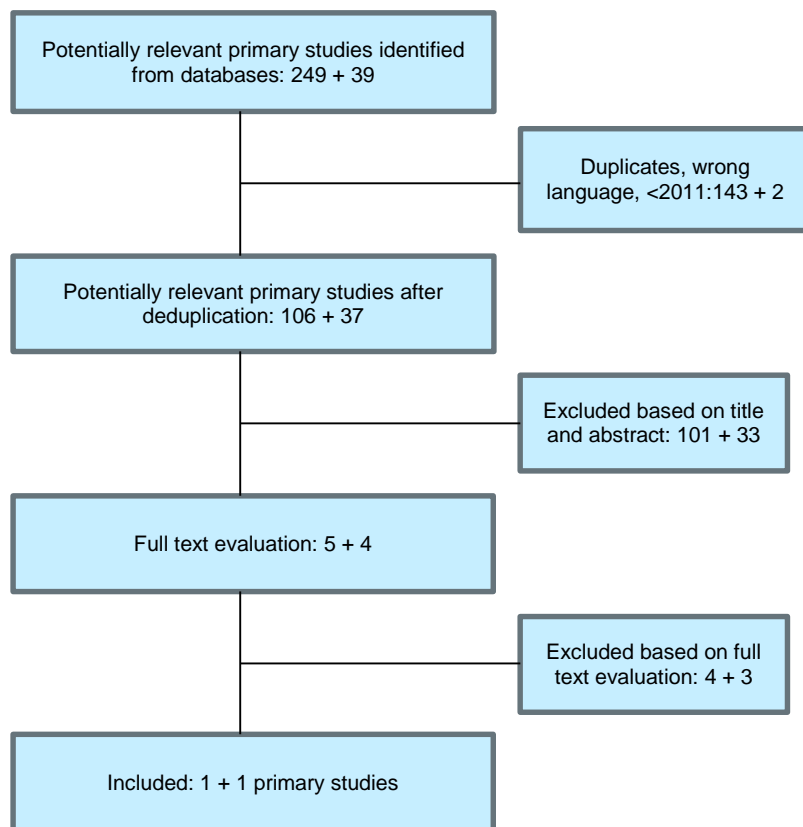
Table 27 – Methodological quality of the included SRs (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of included and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Morrison J 2012	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	N

4.2.8.2. RCTs

On January 13, 2015 a search was performed to identify RCTs comparing neoadjuvant chemotherapy and interval debulking versus upfront debulking followed by chemotherapy in women with advanced ovarian cancer. The search date of Morrison 2012 was used as starting point. MEDLINE (including PreMedline), Embase and CENTRAL were searched, limited from 2011 onwards. In total, 249 potential relevant references were identified (Figure 23). After de-duplication and removal of references in the wrong language or published before 2011, 106 unique references remained. Based on title and abstract 101 studies were excluded. Of the remaining five studies, one study was included and four studies were excluded with reason (Table 28).²⁹³

On September 1, 2015 the search was rerun, and yielded 39 new potential relevant references. After de-duplication, 37 unique references remained. Based on title and abstract 33 studies were excluded. Of the remaining four studies, one study was included and three studies were excluded with reason (Table 29).

**Figure 23 – Study flow of selection of primary studies**

**Table 28 – Excluded RCTs based on full-text evaluation: search January 2015**

Reference	Reason for exclusion
Greimel E, Kristensen G, Vergote I, Hoskins P, Burg MEL, Casado HA, et al. Quality of life in advanced ovarian cancer patients: A randomized phase III study comparing upfront debulking surgery versus neo-adjuvant chemotherapy. <i>International journal of gynecological cancer</i> . 2011;21(12 SUPPL. 3):S620.	Poster
Rowland M, Farris C, Lesnock J, Krivak T. Neoadjuvant chemotherapy is less costly than primary debulking surgery for treatment of advanced stage ovarian cancer in patients > 65 years old. <i>Gynecologic oncology</i> . 2013;131(1):278-9.	Abstract of cost-effectiveness study
van de Laar R, Zusterzeel PL, Van Gorp T, Buist MR, van Driel WJ, Gaarenstroom KN, et al. Cytoreductive surgery followed by chemotherapy versus chemotherapy alone for recurrent platinum-sensitive epithelial ovarian cancer (SOCcer trial): a multicenter randomised controlled study. <i>BMC Cancer</i> . 2014;14(22).	Wrong comparison
Van Meurs H.S, Tajik P, Hof M.H.P, Vergote I, Kenter G.G, Mol B.W.J, et al. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. <i>Eur. J. Cancer</i> . 2013;49(15):3191-201.	Post-hoc analysis of EORTC study

Table 29 – Excluded RCTs based on full-text evaluation: search September 2015.

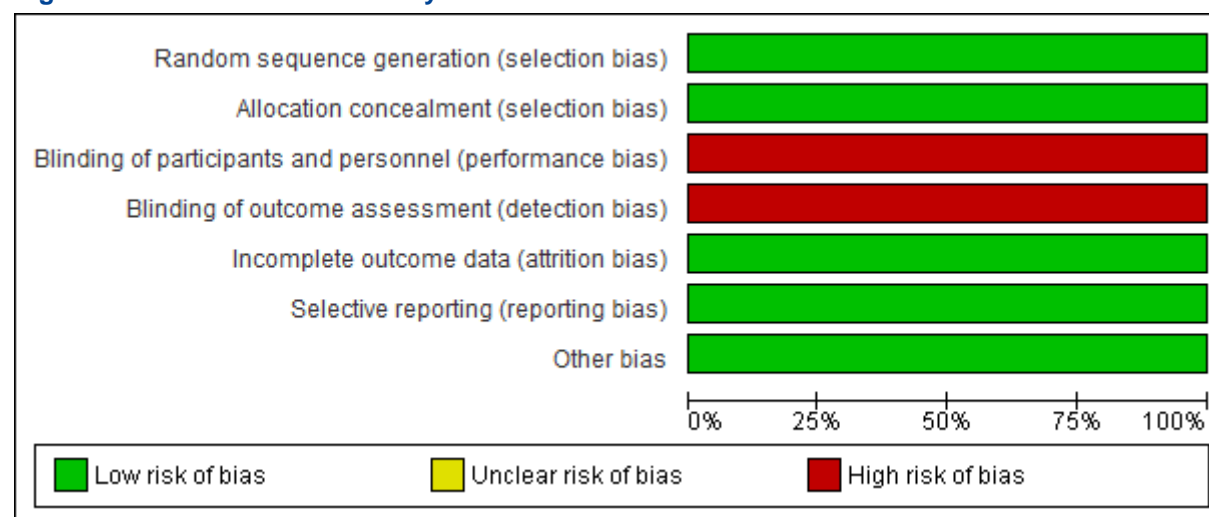
Reference	Reason for exclusion
Onda T, Yoshikawa H, Shibata T, Nakamura K, Satoh T, Saito T, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in phase III randomized trial: JCOG0602. <i>Journal of clinical oncology</i> . 2014;32(15 SUPPL. 1).	Abstract
Rowland MR, Lesnock JL, Farris C, Kelley JL, Krivak TC. Cost-utility comparison of neoadjuvant chemotherapy versus primary debulking surgery for treatment of advanced-stage ovarian cancer in patients 65 years old or older. <i>Am J Obstet Gynecol</i> . 2015;212(6):763.e1-8.	Cost-utility study
Forde GK, Chang J, Ziogas A, Tewari KS, Bristow RE. Primary debulking surgery and neo-adjuvant chemotherapy in the Medicare population: An analysis of cost of care. <i>Gynecologic oncology</i> . 2015;137:109-10.	Abstract of cost of illness study



Quality appraisal of selected RCTs

Figure 24 shows the results of the risk of bias assessment for the included studies.

Figure 24 – Risk of bias summary of RCTs

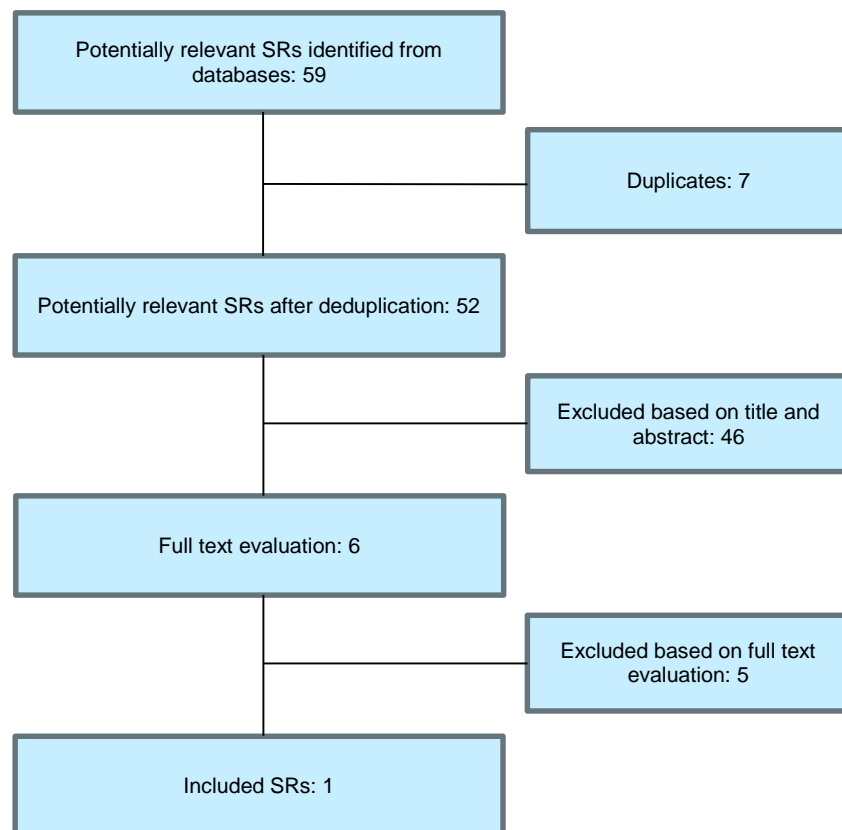


4.2.9. Intra-peritoneal chemotherapy

4.2.9.1. Systematic reviews

On February 23, 2015 a search was performed to identify SRs comparing postoperative intra-peritoneal chemotherapy with standard intravenous chemotherapy in women with advanced ovarian cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched.

In total 59 potential relevant references were identified (Figure 25). After de-duplication 52 unique references remained. Based on title and abstract 46 reviews were excluded. Six reviews were included for full-text evaluation. Of these, five were excluded with reasons (Table 30) and one was included.³⁸³

**Figure 25 – PRISMA flowchart selection of SRs intraperitoneal chemotherapy**

**Table 30 – Intraperitoneal chemotherapy: excluded SRs based on full text selection**

Reference	Reason for exclusion
Han 2014	Abstract
Francis 2014	Abstract
Bharaswadkar 2014	Abstract
Morgan 2013	Guideline without report of systematic review/critical appraisal
Hodeib 2013	Abstract
Jaaback 2011	Included

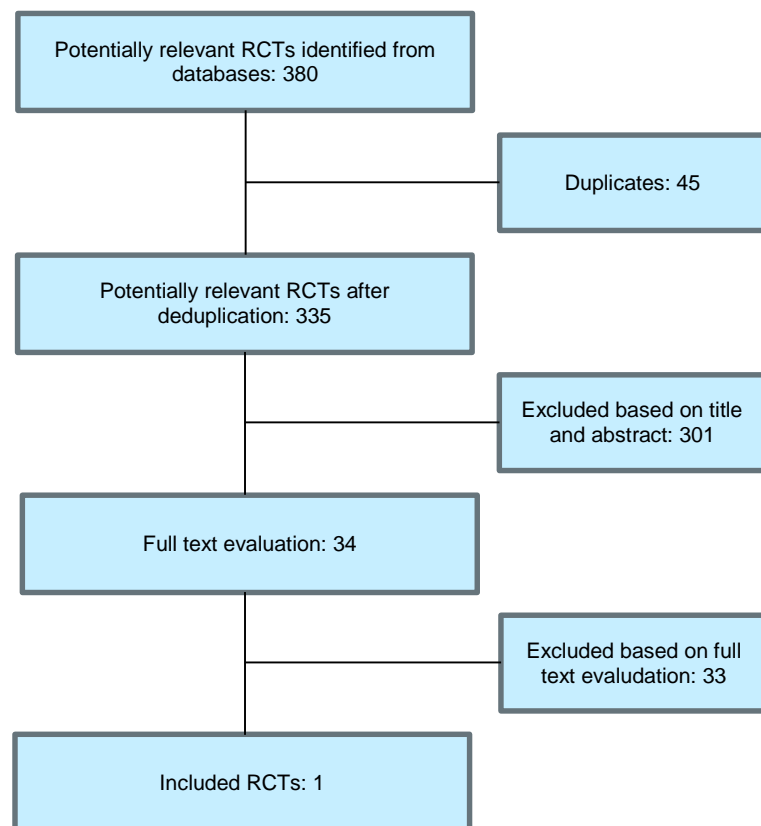
Table 31 shows the results of the risk of bias assessment for the included systematic review, using AMSTAR criteria.

Table 31 – Intraperitoneal chemotherapy: methodological quality of the included SR (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Jaaback K 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	(Y)	N

4.2.9.2. Randomized controlled trials

On February 23, 2015 a search was performed to identify RCTs comparing postoperative intra-peritoneal chemotherapy with standard intravenous chemotherapy in women with advanced ovarian cancer. The search date of Jaaback 2011 was used as starting point. MEDLINE (including PreMedline), Embase and CENTRAL were searched, limited from 2011 onwards. In total, 380 potential relevant references were identified (Figure 26). After de-duplication, 335 unique references remained. Based on title and abstract 301 studies were excluded. Of the remaining 34 studies, 1 study was included and 33 studies were excluded with reason (Table 32).³⁸⁴

**Figure 26 – PRISMA flowchart selection of RCTs intraperitoneal chemotherapy**

**Table 32 – Intraperitoneal chemotherapy: excluded RCTs based on full text selection**

Reference	Reason for exclusion
Zhao 2015	No surgery, both study arms receive IP chemotherapy (cisplatin vs cisplatin + bevacizumab)
Wright 2014	Abstract, no RCT (cohort study)
Schmalfeldt 2014	Abstract, no RCT, HIPEC
Mousavi 2014	Arabic
Massari 2014	HIPEC, cohort study
Kwa 2014	Narrative review
Francis 2014	Abstract of review
Chiva 2014	Review of retrospective data re: HIPEC
Chang 2014	Abstract of SR
Bowles 2014	No RCT (cohort study)
Zhao 2013	Conference abstract
Zhang 2013	Conference abstract, identical to Zhao 2013
Ubago-Pérez 2013	Compares HIPEC with IV/IP chemotherapy
Tsilimparis 2013	No RCT (cohort study)
Simkens 2013	No RCT (case report)
Marth 2013	Abstract of narrative review
Markman 2013	Narrative review
Grosso 2013	Abstract, RCT including HIPEC, no results reported
Fujiwara 2013	Narrative review
von Gruenigen 2012	Included. Additional results QoL GOG 172
Rubino 2012	Narrative review
Fujiwara 2012	Editorial
De Bree 2012	Narrative review
Chan 2012	SR, included
Barlin 2012	No RCT (cohort study)



Reference	Reason for exclusion
Ansaloni 2012	Letter
Sharma 2011	Abstract, no relevant outcomes reported
Mackay 2011	Narrative review
Le 2011	No RCT (retrospective non-randomized comparative study)
Landrum 2011	No RCT (single-arm phase II study)
Fujiwara 2011	Protocol only
Deraco 2011	No RCT, (cohort study)
Cascales 2011	Letter
Armstrong 2011	Discussion paper

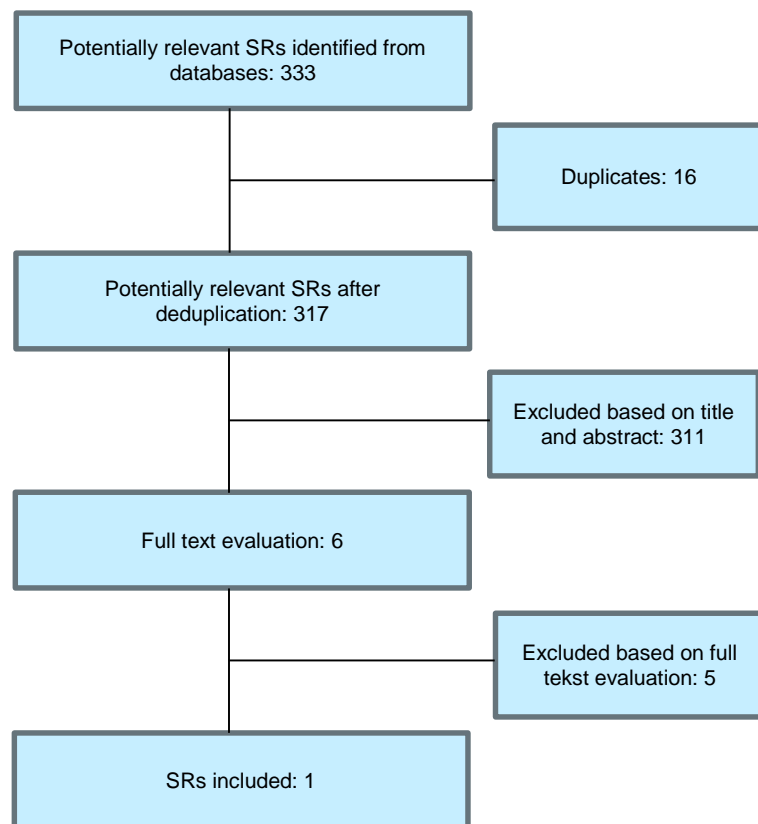
4.2.10. First-line weekly (dose dense) chemotherapy

4.2.10.1. Systematic reviews

On April 15, 2015 a search was performed to identify SRs comparing postoperative intra-peritoneal chemotherapy with standard intravenous chemotherapy in women with advanced ovarian cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched.

In total 333 potential relevant references were identified (Figure 27). After de-duplication 317 unique references remained. Based on title and abstract 311 reviews were excluded. Six reviews were included for full-text evaluation. Of these, five were excluded with reasons (Table 33) and one was included.³⁸⁵

The review of Covens et al. performed a comprehensive search for randomized controlled trials comparing different chemotherapy schedules for first-line treatment of advanced ovarian cancer. No RCT comparing dose dense chemotherapy with 3-weekly administration was identified. The search date of Covens et al. (2001) was used as a starting point for the selection of RCTs.

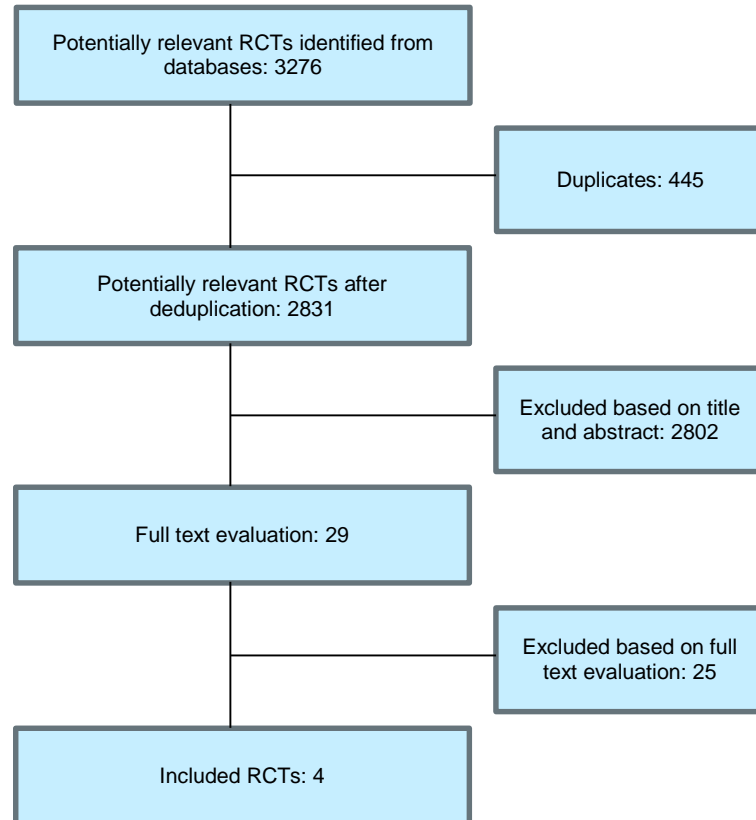
**Figure 27 – PRISMA flowchart selection of SRs weekly (dose dense) chemotherapy**

**Table 33 – Weekly (dose-dense) chemotherapy: excluded SRs based on full text selection**

Reference	Reason for exclusion
Fizazi 2000	Not in epithelial ovarian cancer
Covens 2002	Included as starting point for text selection
Kyrigou 2006	Data on different regimens/schedules only reported in narrative summary
Torri 1993	Not comparison of interest, reference list checked
Ben-David 1995	Not comparison of interest, reference list checked
Stewart 1999	Comparison of interest not included

4.2.10.2. Randomized controlled trials

On April 15, 2015 a search was performed to identify RCTs comparing postoperative intra-peritoneal chemotherapy with standard intravenous chemotherapy in women with advanced ovarian cancer. MEDLINE (including PreMedline), Embase and CENTRAL were searched from inception. In total, 3276 potential relevant references were identified (Figure 28). After de-duplication, 2831 unique references remained. For study selection, the search date of Covens et al. was used as a starting point. Based on publication date, title and abstract 2802 studies were excluded. Of the remaining 29 studies, 4 papers³⁸⁶⁻³⁸⁹ were included and 25 studies were excluded with reason (Table 34). Three³⁸⁶⁻³⁸⁸ of the four publications reported on the same trial, so finally, only two studies (but four publications) were included.

**Figure 28 – PRISMA flowchart selection of RCTs weekly (dose dense) chemotherapy**

**Table 34 – Weekly (dose-dense) chemotherapy: excluded RCTs based on full text selection**

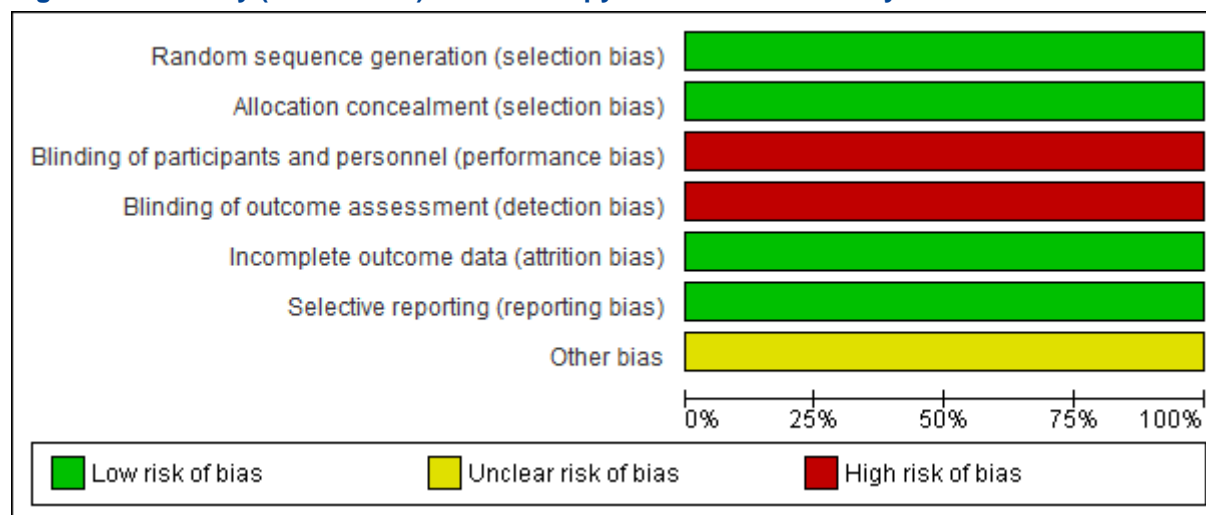
Reference	Reason for exclusion
Wu 2001	Excluded, weekly versus monthly schedules, continued until intolerable toxicity
De Jongh 2002	Excluded, prior platinum-based chemotherapy allowed, dose-escalation study
Samson 2004	Narrative summary of conference
Shen 2005	Excluded, Chinese, possibly duplicate of Shen 2006
Van der Burg 2005	Excluded, Narrative review
Vasey 2005	Excluded, Narrative review
Shen 2006	Excluded, abstract
Spriggs 2007	Excluded, compares two 3-weekly schedules with different infusion durations
Sehouli 2008	Excluded, non-randomized phase I study
Van der Burg 2009	abstract
Katsumata 2009	Included
Fruscio 2011	Excluded, cisplatin monotherapy in both arms
Van der Burg 2011	Excluded, Narrative review
Williams 2011	Excluded, not comparison of interest (long versus short duration of infusion)
Dalton 2012	Cost-effectiveness study, no new data
Gonzalez-Martin 2012	Excluded, Abstract, includes bevacizumab
Katsumata 2012	Excluded, Abstract JGOG 3016 trial
Chan 2013	Excluded, Abstract
Gonzalez-Martin 2013	Excluded, Abstract, includes bevacizumab
Hook 2013	Excluded, Abstract
Katsumata 2013	Included
Pignata 2013	Excluded, Abstract
Harano 2014	Included
Hook 2014	Excluded, Abstract ICON 8
Monk 2014	Excluded, Abstract GOG 262
Pignata 2014	Included



Reference	Reason for exclusion
Slaughter 2014	Narrative review
Van der Burg 2014	Excluded, Only chemotherapy before surgery compares weekly vs 3-weekly, after IDS second randomization to 3 or 6 cycles of 3-weekly chemotherapy
Kumar 2015	Narrative review

Figure 29 shows the results of the risk of bias assessment for the included RCTs

Figure 29 – Weekly (dose-dense) chemotherapy: risk of bias summary of RCTs

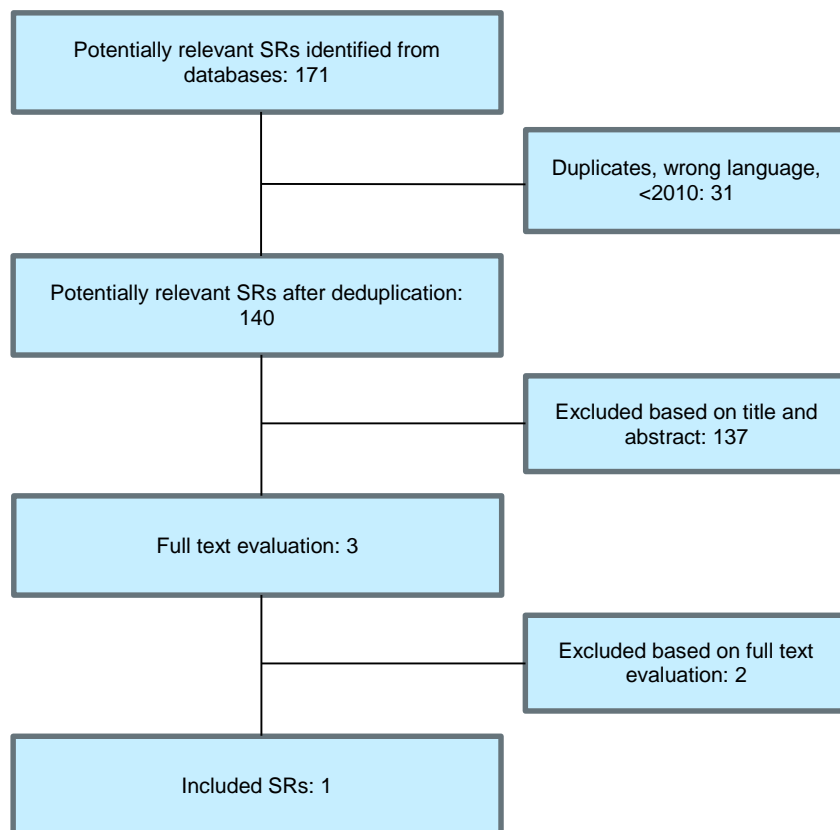


4.2.11. Routine CA125 measurement during follow-up

4.2.11.1. Systematic reviews

On January 27, 2015 a search was performed to identify SRs evaluating routine CA125 measurements during follow-up in women with ovarian cancer. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DaRe) were searched.

In total 171 potential relevant references were identified (Figure 30). After de-duplication and removal of references in the wrong language or published before 2010, 140 unique references remained. Based on title and abstract 137 reviews were excluded. Three reviews were included for full-text evaluation. Of these, two were excluded with reasons (Table 35) and one was included.³⁹⁰

**Figure 30 – CA125 measurements during FU: PRISMA flowchart selection of SRs**

**Table 35 – Routine CA125 measurement during follow-up: excluded SRs based on full-text evaluation**

Reference	Reason for exclusion
Kew F, Galaal K, Bryant A, Naik R. Evaluation of follow-up strategies for patients with epithelial ovarian cancer following completion of primary treatment. Cochrane Database Syst Rev. 2011(6):CD006119	Updated by Clarke T 2014
Geurts SM, de Vegt F, van Altena AM, van Dijck JA, Tjan-Heijnen VC, Verbeek AL, et al. Considering early detection of relapsed ovarian cancer: a review of the literature. Int J Gynecol Cancer. 2011;21(5):837-45	No quality appraisal of included studies

Table 36 shows the results of the risk of bias assessment for the included systematic review, using AMSTAR criteria.

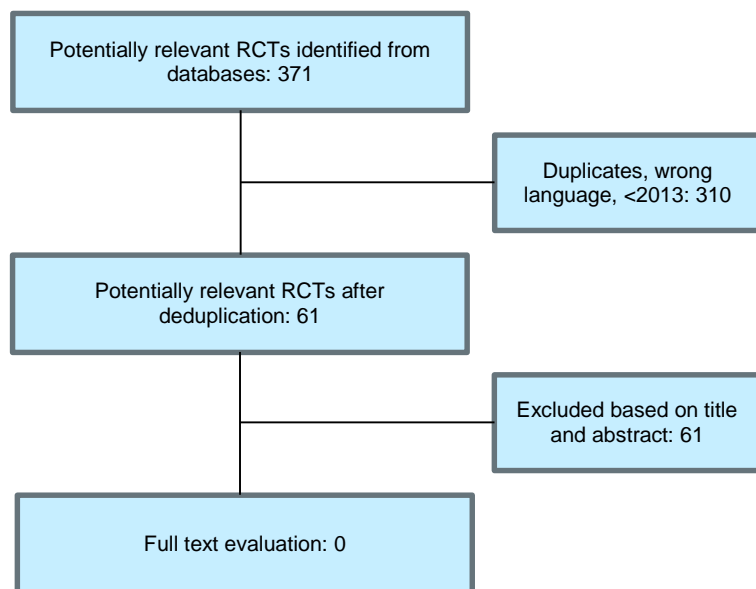
Table 36 – Routine CA125 measurement during follow-up: methodological quality of the included SR (AMSTAR)

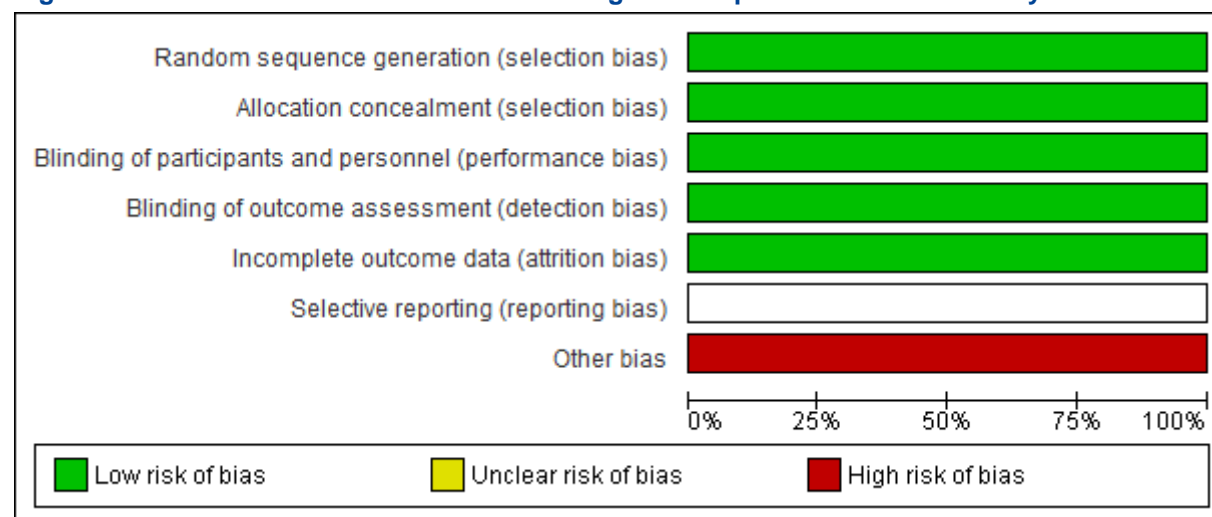
Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Clarke T 2014	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	N

4.2.11.2. Randomized controlled trials

On January 27, 2015 a search was performed to identify RCTs evaluating routine CA125 measurements during follow-up in women with ovarian cancer. The search date of Clarke 2014 was used as starting point. MEDLINE (including PreMedline), Embase and CENTRAL were searched, limited from 2013 onwards. In total, 371 potential relevant references were identified (Figure 31). After de-duplication and removal of references in the wrong language or published before 2013, 61 unique references remained. Based on title and abstract all 61 studies were excluded.

Figure 32 shows the results of the risk of bias assessment for the single RCT³⁹¹ included in Clarke 2014.

**Figure 31 – Routine CA125 measurements during FU: PRISMA flowchart selection of RCTs**

**Figure 32 – Routine CA125 measurement during follow-up: Risk of bias summary of RCTs**



5. EVIDENCE TABLES BY CLINICAL QUESTION

5.1. Pre-operative assessment pelvic mass

Table 37 – Evidence table: SR Pre-operative assessment pelvic mass

Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems (review); Kaijser 2014 ¹	
Methods	
Design	Systematic review and meta-analysis
Source of funding and competing interest	<u>Funding</u> : non-commercial grants from Flanders' Agency for Innovation by Science and Technology, Research foundation Flanders and the National Institute for Health research Biomedical Research centre based at Imperial College Healthcare NHS trust and Imperial College London <u>Col</u> : all authors declare no commercial or financial interest that could appear to have influenced submitted work.
Search date	1 October 2013
Searched databases	Medline (Pubmed), EMBASE (OvidSP)
Included study designs	Diagnostic test accuracy studies, using a prediction model that had been externally validated in at least two different studies on a minimal total sample of 1000 adnexal masses
Number of included studies	195 studies, 23 studies on RMI I
Statistical analysis	If common cut-off point: pooled summary estimate of the expected operating point and corresponding 95%CI obtained using a bivariate random effects model using the PROC GLIMMIX procedure in SAS9.2 If variation in cut-off points: bivariate hierarchical summary receiver operating curve (HSROC) model was fitted using the PROC NLMIXED procedure in SAS9.2 to estimate the summary ROC curve
Patient characteristics	
Eligibility criteria	Women presenting with adnexal mass
Exclusion criteria	Studies limited to children, adolescents or pregnant women. Studies that evaluated model performance only for very specific histological subgroups of ovarian cancer (i.e. non-epithelial ovarian cancer, BOTs) Studies that tested models in a screening setting
Patient & disease characteristics	All 19 models combined had been tested on a total of 26 438 adnexal tumours including 27% malignant and 73% benign tumours.

**Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems (review); Kaijser 2014¹****Interventions**

Index test	Risk of malignancy index I or other risk model
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Target condition	Ovarian borderline or invasive cancer
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Reference standard	histopathology
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Results

Sensitivity	RMI 1: 0.72 [95%CI 0.67-0.76] RMI 2: 0.75 [95%CI 0.75-0.80]] IOTA simple rules: 0.93 [0.89-0.95]
-------------	--

Specificity	RMI 1: 0.92 [95%CI 0.89-0.93] RMI 2: 0.87 [95%CI 0.84-0.90] IOTA simple rules: 0.81 [95%CI 0.76-0.85]
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Notes

Limitations	Comparative accuracy between considered tests not restricted to studies that have evaluated the tests/models in the same individuals. 41% of studies were retrospective in design.
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5.2. Intra-operative frozen section

Table 38 – Evidence table (1): DTA study frozen section

Intraoperative Frozen Section in Ovarian Neoplasms; A Tertiary Center Experience; Açikalin 2014 ³⁹²	
Methods	
Design	Retrospective DTA study
Source of funding and competing interest	Source of funding not reported Competing interests not disclosed
Setting	Single, tertiary care centre, Turkey
Sample size	N=282
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative frozen section (FS) for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	Re-analysis of charts of 282 women with an ovarian neoplasm (42.8% of all gynaecologic FSs) with intraoperative FS reports diagnosed between July 2006 and January 2013. Paraffin section diagnoses with non-tumoural ovarian lesions (massive ovarian oedema, haemorrhagic necrosis, benign cysts, infections) were excluded.
Patient characteristics	Median age: 44.9 (range 12-80) years Tumour type Epithelial tumours 235 (83.3%); 85 considered benign, 24 borderline and 126 malignant; Sex-cord stromal tumours 39 (13.8%) Germ cell tumours 8 (2.8%) “All cases were diagnosed as benign, borderline (for epithelial tumours) or malignant on FS. Sub-categorization, in terms of histologic type, primary or metastasis was not possible in some cases of FS.”
Prevalence of disease	Malignant lesions: 138/282 (48.9%) Malignant and borderline lesions: 162/282 (57.4%)
Interventions	
Index test(s)	Intraoperative frozen section.



Intraoperative Frozen Section in Ovarian Neoplasms; A Tertiary Center Experience; Açikalin 2014³⁹²

“All fresh gross specimen were examined by a resident and a pathologist or particularly gynaecopathologist, in terms of localization, size, colour, content, heterogeneity, infiltration pattern of the tumour and condition of the ovarian capsule. One to four sections depending on the size and heterogeneity of the tumour were sampled in a cryostat and sections were stained by haematoxylin-eosin. Slides were evaluated and reported to the surgeon by the pathologist. Final PS diagnosis reported by an experienced gynaecopathologist was accepted as accurate diagnose.”

Reference standard Paraffin section (not further specified).

Results

Diagnostic accuracy (sensitivity, specificity) Target condition: malignant ovarian tumour
Sensitivity: 0.96 (95%-CI 0.91 to 0.98)
Specificity: 1.00 (95%-CI 0.97 to 1.00)

Target condition: malignant or borderline ovarian tumour
Sensitivity: 0.98 (95%-CI 0.94 to 0.99)
Specificity: 0.97 (95%-CI 0.93 to 0.99)

Limitations and other comments

Limitations Retrospective study, based on having had FS and PS. Unclear risk of bias for Patient Selection, Index Test and Reference Standard; unclear applicability concerns for Patient Selection, Index Test and Reference Standard.

Table 39 – Evidence table (2): DTA study frozen section

Frozen section diagnoses of 578 ovarian tumors made by pathologists with and without expertise on gynecologic pathology; Bige 2011³⁹³

Methods

Design	Retrospective DTA study
Source of funding and competing interest	Source of funding: not reported Competing interests: none declared
Setting	Single centre study (Departments of pathology and Obstetrics and Gynecology, Gynecologic Oncology Group, Dokuz Eylul University School of Medicine, Izmir, Turkey)



Frozen section diagnoses of 578 ovarian tumors made by pathologists with and without expertise on gynecologic pathology; Bige 2011³⁹³

Sample size	N=578 women operated with the suspicion of ovarian neoplasms; 519 analysed (definitive diagnosis of 14 patients (2.4%) could not be obtained; in 23 patients, no ovarian issue could be identified; in 22 cases, metastasis to the ovaries was detected "but there were no discordance between the pathologists").
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated. Subgroups of results of frozen section diagnosis by gynaecological pathologists (Group 1) and non-gynaecological pathologists (Group 2) were also compared.
Patient characteristics	
Eligibility criteria	Retrospective analysis of reports of frozen section diagnosis of 578 patients who underwent surgery for ovarian tumours between January 2002 and December 2010. Indications of frozen section diagnosis were radiologically or macroscopically benign appearing ovarian masses with high Ca125 values, history of malignancy other than ovary and fertility preserving surgery for young women.
Patient characteristics	Mean age (range) in years: benign 41 (13–82), borderline 45 (25–63) and malignant 53 (24–74) Tumour type: not reported. Deferred cases: 14/578 (2.4%)
Prevalence of disease	Malignant lesions: 121/519 (23.3%) Malignant and borderline lesions: 148/519 (28.5%)
Interventions	
Index test(s)	Intraoperative frozen section (categories: primary epithelial ovarian tumour (benign, borderline and malignant); primary ovarian germ cell tumour, ovarian metastatic carcinoma, benign non-neoplastic lesions and no definitive diagnosis). "Following incision to the abdomen either by laparoscopy or by laparotomy, the unfixed fresh masses were delivered immediately to the pathologist with a detailed form including all of the clinical findings of the patient. After macroscopic examination, two to five sections especially from solid areas were obtained according to the type and size of the mass. Frozen procedures were performed through cryostat. The sections were 7–8 µm in thickness and were stained with haematoxylin-eosin. Meanwhile, the imprint was conducted. All of the stained sections were examined under the light microscope by at least two pathologists who were consultants of that month in question."
Reference standard	Paraffin block. "Paraffin blocks were prepared for the final diagnosis from the sections obtained from each 1 cm of the greatest diameter of the mass. Sections 4-5 µm in thickness were obtained from these paraffin blocks. Thereafter these sections were stained with haematoxylin-eosin and examined."



Frozen section diagnoses of 578 ovarian tumors made by pathologists with and without expertise on gynecologic pathology; Bige 2011³⁹³

Results

Diagnostic accuracy (sensitivity, specificity)

Target condition: malignant ovarian tumour

Sensitivity: 0.95 (95%-CI 0.90 to 0.98)

Specificity: 0.99 (95%-CI 0.97 to 1.00)

Target condition: malignant or borderline ovarian tumour

Sensitivity: 0.97 (95%-CI 0.93 to 0.99)

Specificity: 0.99 (95%-CI 0.98 to 1.00)

Limitations and other comments

Limitations

Retrospective study, based on having had FS and PS. Unclear risk of bias for Patient Selection and Reference Standard; high applicability concerns for Patient Selection.

Table 40 – Evidence table (3): DTA study frozen section

Intra-operative frozen section analysis for suspected early-stage ovarian cancer: 11 years of Gateshead Cancer Centre experience; Cross 2012³⁹⁴

Methods

Design	Prospective DTA database study (based on prospectively collected data)
Source of funding and competing interest	Source of funding: none Competing interests: none declared
Setting	Single centre study (Northern Gynaecological Oncology Centre and Department of Cellular Pathology, Gateshead, UK)
Sample size	N=1,445; 1,439 analysed
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values and likelihood ratios of intraoperative FS for benign, borderline and malignant lesions were calculated.

Intra-operative frozen section analysis for suspected early-stage ovarian cancer: 11 years of Gateshead Cancer Centre experience; Cross 2012³⁹⁴

Patient characteristics

Eligibility criteria	Ovarian lesions sent for routine intra-operative FS between January 2000 and December 2010 for suspected ovarian cancer. Any other non-ovarian FSs (e.g. lymph nodes, non-ovarian masses) were excluded. Six deferred cases were excluded from the overall analysis.
Patient characteristics	Mean age: not reported Tumour type Serous 486 (33.8%) Mucinous 267 (18.6%) Endometrioid 151 (10.5%) Clear cell 58 (4.0%) Urothelial/Brenner 20 (1.4%) Germ cell 78 (5.4%) Sex-cord stromal 138 (9.6%) Secondary tumour diagnoses 69 (4.8%) "Benign frozen section ovarian mass diagnoses" 169 (11.7%) Not mentioned: 3 Deferred cases: 6/1,445 (0.4%)
Prevalence of disease	Malignant lesions: 516/1,439 (35.9%) Malignant and borderline lesions: 659/1,439 (45.8%)
Interventions	
Index test(s)	Intraoperative frozen section. "The specimen, once removed, is transported by a hospital porter direct to the histology laboratory and handed over to the laboratory staff. The pathologist on duty inspects the specimen and, after describing it, routinely takes up to two pieces of tissue for FS analysis. These are then processed and, after hand staining, are given to the duty pathologist for reporting. The result is then telephoned to the surgeon involved in the operating theatre. The FS (and subsequent paraffin section) is reported by one of five experienced consultant histopathologists. Two of these act as leads for gynaecological pathology reporting, but all five take part in the routine reporting of the FS on a rota basis."
Reference standard	Paraffin block (not further specified).



Intra-operative frozen section analysis for suspected early-stage ovarian cancer: 11 years of Gateshead Cancer Centre experience; Cross 2012³⁹⁴

Results

Diagnostic accuracy (sensitivity, specificity)

Target condition: malignant ovarian tumour
Sensitivity: 0.80 (95%-CI 0.77 to 0.84)
Specificity: 0.99 (95%-CI 0.99 to 1.00)

Target condition: malignant or borderline ovarian tumour
Sensitivity: 0.91 (95%-CI 0.89 to 0.93)
Specificity: 0.99 (95%-CI 0.97 to 0.99)

Limitations and other comments

Limitations Unclear risk of bias for Reference Standard.

Table 41 – Evidence table (4): DTA study frozen section

Accuracy of Intra-operative Frozen Section Analysis of Ovarian Tumours; Gorisek 2009³⁹⁵

Methods

Design	Retrospective DTA study
Source of funding and competing interest	Source of funding: not reported Competing interests: none declared
Setting	Single centre study (Maribor Teaching Hospital, Department of Gynaecologic Oncology, Slovenia)
Sample size	N=131
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated

Patient characteristics

Eligibility criteria	Women treated for benign, borderline and malignant ovarian tumours between 1 January 1993 and 31 December 2001
Patient characteristics	Mean age: not reported. Tumour type



Accuracy of Intra-operative Frozen Section Analysis of Ovarian Tumours; Gorisek 2009³⁹⁵

	<p>Serous 94 (72%)</p> <p>Mucinous 13 (10%)</p> <p>Endometrioid 13 (10%)</p> <p>Other 11 (8%)</p> <p>Deferred cases: not reported</p>
Prevalence of disease	<p>Malignant lesions: 82/131 (62.6.%)</p> <p>Malignant and borderline lesions: 128/131 (97.7%)</p>
Interventions	
Index test(s)	<p>Intraoperative frozen section.</p> <p>"After tumour removal, the fresh surgical specimen was immediately taken to the Department of Pathologic Morphology at the Maribor Teaching Hospital (now the University Clinical Centre Maribor). A pathologist prepared specimens from representative regions, frozen them in a cryostat and cut slices with a microtome. The slices were mounted on a glass slide, stained with haematoxylin and eosin, and were then ready for microscopic evaluation."</p>
Reference standard	<p>Paraffin block.</p> <p>"Permanent histopathological sections were obtained from a paraffin block containing fixed tissue specimens taken from the tumours, and these were considered to provide an accurate diagnosis."</p>
Results	
Diagnostic accuracy (sensitivity, specificity)	<p>Target condition: malignant ovarian tumour</p> <p>Sensitivity: 0.96 (95%-CI 0.91 to 0.98)</p> <p>Specificity: 1.00 (95%-CI 0.97 to 1.00)</p> <p>Target condition: malignant or borderline ovarian tumour</p> <p>Sensitivity: 0.98 (95%-CI 0.94 to 0.99)</p> <p>Specificity: 0.97 (95%-CI 0.93 to 0.99)</p>
Limitations and other comments	
Limitations	<p>Retrospective study, based on having had FS and PS. Unclear risk of bias for all domains; unclear applicability concerns for Patient Selection and Index Test. Very low percentage of benign lesions.</p>

**Table 42 – Evidence table (5): DTA study frozen section**

Accuracy of intra-operative frozen section in the diagnosis of ovarian tumours; Ilker 2011 ³⁹⁶	
Methods	
Design	Retrospective DTA study
Source of funding and competing interest	Source of funding: not reported Competing interests: not reported
Setting	Single centre study (Zonguldak Maternity Hospital, Zonguldak, Turkey)
Sample size	N=278; N=266 analysed
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	Women who underwent surgery for ovarian masses and on whom frozen section was performed between January 2002 and December 2008. Twelve patients (4.3%) for whom a definitive result was not obtained from FS were excluded..
Patient characteristics	Mean age: 42.5 (\pm 13.5) years Tumour type Epithelial tumours 16 (6.0%) Germ cell tumours 10 (3.8%) Other malignant tumours 2 (0.8%) Borderline tumours 9 (3.4%) Benign tumours 229 (86.1%) Deferred cases: 12/278 (4.3%)
Prevalence of disease	Malignant lesions: 28/266 (10.5%) Malignant and borderline lesions: 37/266 (13.9%)
Interventions	
Index test(s)	Intraoperative frozen section.



Accuracy of intra-operative frozen section in the diagnosis of ovarian tumours; Ilker 2011³⁹⁶

		“Each specimen collected from the operation site was transferred to the pathology unit with the patient's clinical details as soon as possible. The size and the presence of surface irregularities and vegetations were then macroscopically evaluated. Two to five samples taken from suspicious areas were frozen, cut into 5 µm sections, and stained with haematoxylin and eosin. Both frozen and paraffin sections were examined by expert pathologists.”
Reference standard		Paraffin block (not further specified).
Results		
Diagnostic accuracy (sensitivity, specificity)		<p>Target condition: malignant ovarian tumour</p> <p>Sensitivity: 0.71 (95%-CI 0.51 to 0.87)</p> <p>Specificity: 1.00 (95%-CI 0.98 to 1.00)</p> <p>Target condition: malignant or borderline ovarian tumour</p> <p>Sensitivity: 0.84 (95%-CI 0.68 to 0.94)</p> <p>Specificity: 1.00 (95%-CI 0.98 to 1.00)</p>
Limitations and other comments		
Limitations		Retrospective study, based on having had FS and PS. High risk of bias for Patient Selection; unclear risk of bias for Reference Standard; high applicability concerns for Patient Selection.

Table 43 – Evidence table (6): DTA study frozen section

The accuracy of frozen section diagnosis in apparent early ovarian cancer – results from a UK centre; Kokka 2009³⁹⁷

Methods		
Design		Retrospective DTA study
Source of funding and competing interest		<p>Source of funding: Griffiths Foundation</p> <p>Competing interests: not reported</p>
Setting		Single centre study (Departments of Gynaecologic Oncology and Cellular Pathology, Clinical Effectiveness Audit Coordinator Barts and the London NHS Trust, London, UK)
Sample size		N=50 (FS was considered in 71 patients; ten cases were excluded because of valid reasons; in 11 of 31 benign tumours FS was not requested by the surgeon)



The accuracy of frozen section diagnosis in apparent early ovarian cancer – results from a UK centre; Kokka 2009³⁹⁷

Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	<p>“Between October 2006 and May 2008 FS was considered in 71 patients with suspected early ovarian cancer. Ten cases were excluded: three because of extensive ovarian disease at laparotomy that had not been detected on preoperative imaging and seven because of non-ovarian neoplasms diagnosed through operative findings (three cases) or FS (four cases).”</p> <p>“Furthermore, an experienced surgeon is likely to identify certain types of benign ovarian masses on inspection alone, without using FS. Accordingly, in 11/31 benign tumours FS was not requested.”</p>
Patient characteristics	<p>Mean age: 54 years (range not reported)</p> <p>Tumour type</p> <p>Serous 25 (40.9%)</p> <p>Mucinous 17 (27.9%)</p> <p>Clear cell 4 (6.6%)</p> <p>Endometrioid 1 (1.6%)</p> <p>Sarcoma 1 (1.6%)</p> <p>Other 13 (21.3%)</p> <p>RMI: 10 RMI <25, 35 RMI 25-250, 16 RMI >250</p> <p>Deferred cases: not reported</p>
Prevalence of disease	<p>Malignant lesions: 20/50 (40.0%)</p> <p>Malignant and borderline lesions: 30/50 (60.0%)</p>
Interventions	
Index test(s)	Intraoperative frozen section (not specified).
Reference standard	Paraffin block (not further specified).
Results	
Diagnostic accuracy (sensitivity, specificity)	NB: accuracy parameters calculated for 50 out of 61 cases in which FS was deemed necessary



The accuracy of frozen section diagnosis in apparent early ovarian cancer – results from a UK centre; Kokka 2009³⁹⁷

Target condition: malignant ovarian tumour

Sensitivity: 0.95 (95%-CI 0.75 to 1.00)

Specificity: 1.00 (95%-CI 0.88 to 1.00)

Target condition: malignant or borderline ovarian tumour

Sensitivity: 0.93 (95%-CI 0.78 to 0.99)

Specificity: 0.90 (95%-CI 0.68 to 0.99)

Limitations and other comments

Limitations

Retrospective study, based on having had FS and PS (letter to the editor). Unclear risk of bias for Index Test and Reference Standard; no applicability concerns.

Table 44 – Evidence table (7): DTA study frozen section

How accurate is intraoperative frozen section in the diagnosis of ovarian tumors? Malipatil 2013³⁹⁸

Methods

Design	Retrospective DTA study
Source of funding and competing interest	Source of funding: none Competing interests: none declared
Setting	Single centre study (Department of Pathology, St. John's Medical College, Bangalore, India)
Sample size	N= 218 (N=377 referrals for diagnosis; intraoperative diagnosis sought in 233 (apparently 223?) cases; diagnosis deferred in five cases due to extensive areas of haemorrhage and necrosis and was excluded from further analysis; 218 cases analysed)
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	Not specified. "Frozen and permanent section reports of ovarian tumours referred to the department over a period of 10 years from 1999 to 2008 were retrieved."
Patient characteristics	Mean age: 42.8 (range 11 to 75) years

**How accurate is intraoperative frozen section in the diagnosis of ovarian tumors? Malipatil 2013³⁹⁸**

	Tumour type Epithelial tumours 165 (74.0%) Sex-cord stromal tumours 15 (6.7%) Germ cell tumours 30 (13.5%) Metastasis 7 (3.1%) Other 1 (0.4%) Deferred cases: 5/223 (2.2%)
Prevalence of disease	Malignant lesions: 53/218 (24.3%) Malignant and borderline lesions: 68/218 (31.2%)
Interventions	
Index test(s)	Intraoperative frozen section. "At least two general surgical pathologists were routinely involved in frozen section diagnosis."
Reference standard	Paraffin section (not further specified).
Results	
Diagnostic accuracy (sensitivity, specificity)	Target condition: malignant ovarian tumour Sensitivity: 0.85 (95%-CI 0.72 to 0.93) Specificity: 1.00 (95%-CI 0.98 to 1.00)
	Target condition: malignant or borderline ovarian tumour Sensitivity: 0.93 (95%-CI 0.84 to 0.98) Specificity: 0.99 (95%-CI 0.96 to 1.00)
Limitations and other comments	
Limitations	Retrospective study, based on having had FS and PS. High risk of bias for Patient Selection; unclear risk of bias for Reference Standard; high applicability concerns for Patient Selection. NB: calculation errors. N=377 referrals for diagnosis; intraoperative diagnosis sought in 233 cases (must be 223); diagnosis deferred in five cases due to extensive areas of hemorrhage and necrosis and was excluded from further analysis. 218 analysed. Also in Table 1 calculation errors.


Table 45 – Evidence table (8): DTA study frozen section

Accuracy of frozen section diagnosis in ovarian masses: experience at a tertiary oncology center; Rakhshan 2009 ³⁹⁹	
Methods	
Design	Retrospective DTA study
Source of funding and competing interest	Source of funding: not reported Competing interests: none declared
Setting	Single centre study (Department of Pathology, Shohada Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran)
Sample size	N=282
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	Ovarian masses submitted for frozen section from March 1994 to May 2008.
Patient characteristics	Mean age: 44 (range 13 to 78) years Tumour type Epithelial tumours 158 (56.0%) Sex-cord stromal tumours 19 (6.8%) Germ cell tumours 39 (13.8%) Non-neoplastic lesions 53 (18.8%) Metastasis: 7 (2.5%) Other 6 (2.1%) Deferred cases: 0/282 (0%)
Prevalence of disease	Malignant lesions: 65/282 (23.0%) Malignant and borderline lesions: 80/282 (28.4%)
Interventions	
Index test(s)	Intraoperative frozen section.



Accuracy of frozen section diagnosis in ovarian masses: experience at a tertiary oncology center; Rakhshan 2009³⁹⁹

		<p>“In all specimens, after gross examination, one to five sections depending on the tumour size and the degree of suspicion were frozen in a cryostat. Then 5 µm sections were stained with haematoxylin and eosin, and were interpreted by one of the five attending general pathologists.”</p> <p>“All frozen section specimens were reviewed by a pathology resident and an attending surgical pathologist expert in gynaecologic pathology.”</p>
Reference standard		Paraffin sections (not further specified).
Results		
Diagnostic accuracy (sensitivity, specificity)		<p>Target condition: malignant ovarian tumour</p> <p>Sensitivity: 0.92 (95%-CI 0.83 to 0.97)</p> <p>Specificity: 1.00 (95%-CI 0.97 to 1.00)</p> <p>Target condition: malignant or borderline ovarian tumour</p> <p>Sensitivity: 0.91 (95%-CI 0.83 to 0.96)</p> <p>Specificity: 1.00 (95%-CI 0.97 to 1.00)</p>
Limitations and other comments		
Limitations		Retrospective study, based on having had FS and PS. Unclear risk of bias for Patient Selection and Reference Standard; unclear applicability concerns for Patient Selection.

Table 46 – Evidence table (9): DTA study frozen section

Accuracy rate of frozen section studies in ovarian cancers: A regional cancer institute experience; Subbian 2013⁴⁰⁰

Methods		
Design		Retrospective DTA study
Source of funding and competing interest		<p>Source of funding: none</p> <p>Competing interests: none declared</p>
Setting		Single centre study (Department of Gynecologic Oncology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India)
Sample size		N=135



Accuracy rate of frozen section studies in ovarian cancers: A regional cancer institute experience; Subbian 2013⁴⁰⁰

Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	Retrospective analysis of reports of frozen section and paraffin block diagnoses of patients undergoing surgery as primary line of therapy for suspected ovarian neoplasms, from March 2004 to January 2006.
Patient characteristics	<p>Mean age: 43.7 (range 13 to 86) years</p> <p>Tumour type</p> <p>Epithelial tumours 77 (60.6%)</p> <p>Sex-cord stromal tumours 7 (5.5%)</p> <p>Germ cell tumours 16 (12.5%)</p> <p>Other 27 (21.2%) of which 11 non-neoplastic</p> <p>Deferred cases: 8/135 (5.9%)</p>
Prevalence of disease	<p>Malignant lesions: 59/117 (50.4%)</p> <p>Malignant and borderline lesions: 75/117 (64.1%)</p>
Interventions	
Index test(s)	<p>Intraoperative frozen section.</p> <p>"All the frozen section diagnoses were made by a team of expert oncopathologists at the institute. Before sectioning, gross examination of the tumour was carried out and frozen section samples were taken from solid or suspicious areas. The number of bits sampled varied from one to three (average of two). The frozen section and the permanent section reports of each patient were compared. The frozen section results were divided into the following groups: Deferred, benign, borderline and malignant. Reports mentioned as 'suggestive of', 'suspicious of' or 'compatible with' were included in the diagnoses mentioned."</p>
Reference standard	Paraffin block (not further specified).
Results	
Diagnostic accuracy (sensitivity, specificity)	<p>2*2 Tables reconstructed!</p> <p>Target condition: malignant ovarian tumour</p> <p>Sensitivity: 0.92 (95%-CI 0.81 to 0.97)</p> <p>Specificity: 0.98 (95%-CI 0.91 to 1.00)</p>



Accuracy rate of frozen section studies in ovarian cancers: A regional cancer institute experience; Subbian 2013⁴⁰⁰

Target condition: malignant or borderline ovarian tumour

Sensitivity: 0.83 (95%-CI 0.72 to 0.90)

Specificity: 0.90 (95%-CI 0.77 to 0.97)

Limitations and other comments	
Limitations	Retrospective study, based on having had FS and PS. Unclear risk of bias for Patient Selection, Reference Standard and Flow and Timing; no applicability concerns.

Table 47 – Evidence table (10): DTA study frozen section

Role of Frozen Section in Intraoperative Assessment of Ovarian Masses: a Tertiary Oncology Center Experience; Sukumaran 2014⁴⁰¹

Methods	
Design	Retrospective DTA study
Source of funding and competing interest	Source of funding: not reported Competing interests: not reported
Setting	Single centre study (Divisions of Pathology and Surgical Oncology, Regional Cancer Centre, Trivandrum, Kerala, India)
Sample size	N=233
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	Women with ovarian masses in which intraoperative frozen section examination was performed between 2009 and 2012. Cases suffering from torsion with extensive haemorrhage and infarction were excluded.
Patient characteristics	Mean age: 46 (range 14 to 86) years Tumour type Epithelial tumours 153 (11.6%) Sex-cord stromal tumours 16 (6.9%) Germ cell tumours 30 (12.9%)



Role of Frozen Section in Intraoperative Assessment of Ovarian Masses: a Tertiary Oncology Center Experience; Sukumaran 2014⁴⁰¹

		Non-neoplastic lesions 27 (11.6%) Metastasis: 7 (3.0%) Mean tumour size: 14 (range 3 to 36) cm. Deferred cases: 4/237 (1.7%)
Prevalence of disease		Malignant lesions: 88/233 (37.8%) Malignant and borderline lesions: 114/233 (48.9%)
Interventions		
Index test(s)		Intraoperative frozen section. "After gross examination, two to five sections were taken depending on the size and heterogeneity of the lesions. Sections of 4-5 microns were taken and rapid haematoxylin and eosin staining was done. After the frozen section analysis tissues were put in formalin and routine processing was done."
Reference standard		Paraffin section (not further specified).
Results		
Diagnostic accuracy (sensitivity, specificity)		Target condition: malignant ovarian tumour Sensitivity: 0.83 (95%-CI 0.73 to 0.90) Specificity: 0.99 (95%-CI 0.96 to 1.00)
		Target condition: malignant or borderline ovarian tumour Sensitivity: 0.96 (95%-CI 0.91 to 0.99) Specificity: 0.99 (95%-CI 0.95 to 1.00)
Limitations and other comments		
Limitations		Retrospective study, based on having had FS and PS. Unclear risk of bias for Patient Selection, Index Test and Reference Standard; no applicability concerns.

Table 48 – Evidence table (11): DTA study frozen section

Accuracy of frozen section in the diagnosis of ovarian tumours; Toneva 2012⁴⁰²

Methods		
Design		Retrospective DTA study



Accuracy of frozen section in the diagnosis of ovarian tumours; Toneva 2012⁴⁰²

Source of funding and competing interest	Source of funding: not reported Competing interests: none declared
Setting	Single centre study (Department of Obstetrics and Gynaecology, South Essex Gynaecological Oncology Centre, Southend University Hospital NHS Foundation Trust, Westcliff on Sea, Essex, UK)
Sample size	N=66
Time interval between tests	Specimens for FS and PS collected during the same procedure
Statistical analysis	Sensitivity, specificity, positive and negative predictive values of intraoperative FS for benign, borderline and malignant lesions were calculated.
Patient characteristics	
Eligibility criteria	Inclusion from October 2005 to September 2008. Indications for intraoperative frozen section: high RMI; presence of necrotic areas; fragile papillary areas within the cyst; ascites and solid components, which were all thought to represent an increased chance of malignancy.
Patient characteristics	Mean age: 61.4 (\pm 14.8) years Tumour type Serous 48% Mucinous 18.7% Endometriomas 8% Fibromas 5.3% Other 20% Mean tumour size: 14 cm (range 3.5 – 36 cm) Average overall RMI: 719.6 (4 RMI <25, 30 RMI 25-250, 32 RMI >250) Deferred cases: not reported
Prevalence of disease	Malignant lesions: 28/66 (42.4%) Malignant and borderline lesions: 48/66 (72.7%)
Interventions	
Index test(s)	Intraoperative frozen section.

Accuracy of frozen section in the diagnosis of ovarian tumours; Toneva 2012⁴⁰²

“During the operation, the surgeon completed a request form with relevant clinical information and sent the whole ovary/ovaries to be examined for frozen section with no markings attached. The frozen section was performed by the on-call pathologist who was normally a general histopathologist, however, there was always an expert in gynaecological disease available for consultation in difficult cases. On receipt of the specimen, the pathologist initially performed a gross examination of the tumour and identified any solid or suspicious areas. The pathologist then made three to five cuts, depending on the size of the tumour. The specimens were frozen, sliced and stained with haematoxylin and eosin (H&E) and interpreted. The diagnosis of ‘benign’, ‘borderline’ or ‘malignant’ was then communicated to the surgeon via telephone or in person. At our centre, the average time elapsed between sampling and diagnosis was 30-60 min.”

Reference standard

Paraffin block (not further specified).

Results**Diagnostic accuracy
(sensitivity, specificity)**

Target condition: malignant ovarian tumour
Sensitivity: 0.89 (95%-CI 0.72 to 0.98)
Specificity: 1.00 (95%-CI 0.91 to 1.00)

Target condition: malignant or borderline ovarian tumour
Sensitivity: 0.88 (95%-CI 0.75 to 0.95)
Specificity: 1.00 (95%-CI 0.81 to 1.00)

Limitations and other comments**Limitations**

Retrospective study, based on having had FS and PS. Unclear risk of bias for Patient Selection and Reference Standard; no applicability concerns.

5.3. Lymphadenectomy

Table 49 – Evidence table: SR lymphadenectomy

Lymph node metastasis in stages I and II ovarian cancer: a review; Kleppe 2011¹⁴⁴

Methods**Design**

Systematic review

Source of funding and competing interest

No information about source of funding. Authors declare that there are no conflicts of interest.



Lymph node metastasis in stages I and II ovarian cancer: a review; Kleppe 2011¹⁴⁴

Search date	Not reported; the most recent included study is from August 2010
Searched databases	MEDLINE and EMBASE; additional literature was searched through cross-references of the retrieved articles.
Included study designs	Randomized controlled trials, and prospective and retrospective cohort studies.
Number of included studies	N=14; Authors state that there are two RCTs and 12 retrospective cohort studies included. However, we identified two prospective observational studies instead of the two RCTs.
Statistical analysis	Not applicable as only incidences of lymph node metastases are determined.
Patient characteristics	
Eligibility criteria	RCTs, and prospective and retrospective cohort studies that included patients with clinically FIGO stage I or II epithelial ovary carcinoma or a subset of these specific groups; in all patients within the trial or cohort a complete staging laparotomy including a systematic pelvic and para-aortic lymph node dissection (LND) had to be performed.
Exclusion criteria	Not specified, except that it is stated that searches were limited to “full text”, “English” and “human”.
Patient & disease characteristics	In the 14 included studies there were 1247 patients with FIGO stage I-II. The mean number of pelvic and para-aortic lymph nodes removed ranged from 20 to 78. Five studies described the number of removed lymph nodes from the para-aortic and pelvic region separately: the mean number of para-aortic and pelvic lymph nodes ranged from 15 to 46 and 14 to 74, respectively
Interventions	
Surgical procedures	“A complete staging laparotomy including a systematic pelvic and para-aortic lymph node dissection (LND) had to be performed in all patients within the trial or cohort.”
Outcome assessment	No information on outcome assessment in included studies.
Results	
Prevalence of malignant disease in pelvic and para-aortic lymph nodes	<u>Clinical FIGO stage I and II</u> Overall incidence of lymph node metastases (14 studies, n=1247): 177/1247 (14.2%; range 6.1–29.6%) Only para-aortic region: 88/1247 (7.1%; range 3.0–13.0%) Only pelvic region: 36/1247 (2.9%; range 0.0–11.1%) Both para-aortic and pelvic region: 53/1247 (4.3%; range 0.0–14.8%) <i>Incidence of lymph node metastases according to differentiation grade (6 studies, n=361, missing data n=66)</i>

**Lymph node metastasis in stages I and II ovarian cancer: a review; Kleppe 2011¹⁴⁴**

Grade 1: 6/149 (4.0%; range 0.0-6.3%)
Grade 2: 17/103 (16.5%; range 0.0-27.3%)
Grade 3: 10/50 (20.0%; range 0.0-100.0%)

Incidence of lymph node metastases according to histological subtype (8 studies, n=574).

Serous: 35/150 (23.3%; range 8.7-50.0%)
Mucinous: 4/155 (2.6%; range 0.0-6.7%)
Endometrioid: 6/92 (6.5%; range 0.0-20.0%)
Clear cell: 20/139 (14.4%; range 0.0-31.3%)
Undifferentiated / others: 11/38 (28.9%; range 0.0-64.3%)

Clinical FIGO stage I*Incidence of lymph node metastases according to differentiation grade (4 studies, n=188, missing data n=20)*

Grade 1: 2/68 (2.9%; range 0.0-6.3%)
Grade 2: 9/65 (13.8%; range 0.0-27.3%)
Grade 3: 7/35 (20.0%; range 0.0-100.0%)

Incidence of lymph node metastases according to histological subtype (5 studies, n=336)

Serous: 19.3%
Mucinous: 1.9%
Endometrioid: not reported
Clear cell: not reported
Undifferentiated / others: not reported

Unilateral clinical FIGO stages I-II (7 studies)

"In case of lymph node metastases, they were localized only at the contralateral pelvic and para-aortic site in respectively 16.1% and 18.0%."



Lymph node metastasis in stages I and II ovarian cancer: a review; Kleppe 2011¹⁴⁴

Limitations and other comments

Limitations All but two of included studies were retrospective studies, no details of included studies, no quality assessment of included studies.

Table 50 – Evidence table (1): lymphadenectomy

Analysis of para-aortic lymphadenectomy up to the level of the renal vessels in apparent early-stage ovarian cancer; Chang 2013⁶¹

Methods

Design	Retrospective analysis of medical records
Source of funding and competing interest	Source of funding: one of the authors was supported by the Queen of Hearts Foundation Authors report no potential conflict of interest relevant to this article
Setting	Single centre: Ajou University Hospital, Korea
Sample size	N=124
Duration	Medical records from January 1, 2000 through December 31, 2011 were retrospectively reviewed.
Statistical analysis	Patients who underwent systematic pelvic and para-aortic lymphadenectomy were compared to those who did not. The chi-square or Fisher's exact test were used for comparison of observed frequencies. Student t-test or Mann-Whitney U-test were applied for comparison of continuous variables. Kaplan-Meier method was used to estimate progression-free and overall survival rates and the log-rank to compare survival functions. A logistic regression model was performed for multivariate analysis and used in estimating the odds ratios of various parameters which were found to be significant in the univariate analysis. Backward stepwise model-selection methods, using a cut-off p-value of 0.05, were used to select factors that were included in the multivariate analysis. Statistical significance was defined as $p < 0.05$.

Patient characteristics

Eligibility criteria	Ovarian cancer that was thought to be confined to the ovary without any extra-ovarian metastatic lesions at the time of preoperative imaging studies
Exclusion criteria	Not specified
Patient & disease characteristics	Median age: 46 yrs (range 19 to 74) FIGO stage: I: n=87 (70.2%); IA: n=54, IB: n=2, IC: n=31

Analysis of para-aortic lymphadenectomy up to the level of the renal vessels in apparent early-stage ovarian cancer; Chang 2013⁶¹

II: n=19 (15.3%); IIA: n=4, IIB: n=6, IIIC: n=9
III: n=18 (14.5%); IIIA: n=1, IIIB n=0, IIIC: n=17

Patients with systematic lymphadenectomy (n=86, of which n=69 pelvic and para aortic lymphadenectomy) vs. patients without systematic lymphadenectomy (n=38)

Mean/median* age (range): 47.5 yrs (19-74) vs. 45 yrs (19-72)

Mean/median parity (range): 2 (0-7) vs. 1 (0-4)

Mean/median BMI: 23.1 kg/m² (14.4-35.2) vs. 25.4 kg/m² (7.9-28.3)

FIGO stage: IA: 33 (38.4%) vs. 21 (55.3%); IB: 2 (2.3%) vs. 0; IC: 20 (23.3%) vs. 11 (28.9%); IIA: 3 (3.5%) vs. 1 (2.6%); IIB: 3 (3.5%) vs. 3 (7.9%); IIC: 7 (8.1%) vs. 2 (5.3%); IIIA: 1 (1.2%) vs. 0; IIIB 0 vs. 0; IIIC: 17 (19.8%) vs. 0

Histology: serous: 35 (40.7%) vs. 7 (18.4%); mucinous: 16 (18.6%) vs. 16 (42.1%); endometrioid: 8 (9.3%) vs. 4 (10.5%); clear cell: 16 (18.6%) vs. 6 (15.8%); mixed: 9 (10.5%) vs. 3 (7.9%); others: 2 (2.4%) vs. 2 (5.2%)

Tumour grade: grade 1: 37 (43.0%) vs. 24 (63.2%); grade 2: 19 (22.1%) vs. 5 (13.2%); grade 3: 29 (33.7%) vs. 7 (18.4%); unknown: 1 (1.2%) vs. 2 (5.3%)

Mean/median preoperative serum CA-125 (range): 108.9 U/mL (3.5-15,600.0) vs. 87.4 U/mL (6.0-1,722.0)

Presence of ascites: 36 (41.9%) vs. 7 (18.4%)

“Patients with systematic lymphadenectomy had higher parity (p<0.01), more frequent ascites (p=0.01), and higher numbers of resected lymph nodes (p<0.01). There were no statistically significant differences in demographic features, FIGO stage, tumour histology, tumour grade, and preoperative CA-125 level between the two groups.”

*not specified whether mean or median is presented

Interventions**Surgical procedures**

Surgical staging according to the FIGO system. Standard surgical staging procedures included total abdominal hysterectomy (n=104, 83.9%), unilateral or bilateral salpingo-oophorectomy (n=20, 16.1%), peritoneal washings for cytology (n=124, 100%), infracolic omentectomy (n=120, 96.8%), multiple biopsies of pelvic and abdominal peritoneum (n=117, 94.4%) pelvic lymphadenectomy (n=86, 69.4%), and para-aortic lymphadenectomy (n=69, 55.6%).

Pelvic lymphadenectomy included bilateral resection of the common iliac nodes, presacral nodes, external iliac nodes, internal iliac nodes, deep inguinal nodes, and obturator nodes.

**Analysis of para-aortic lymphadenectomy up to the level of the renal vessels in apparent early-stage ovarian cancer; Chang 2013⁶¹**

	Para-aortic lymphadenectomy included removal of all nodal tissues over the vena cava and aorta from the aortic bifurcation to the level of the renal vessels. Median number of harvested lymph nodes (range): pelvic: 25 (10-53); para-aortic: 10 (5-29)
Outcome assessment	All pelvic lymph nodes were separately sent to pathology with dividing into the right and left pelvic lymph nodes. Most of the para-aortic lymph nodes were separately sent to the intraoperative frozen section or postoperative permanent section for pathologic evaluation with dividing into low and high para-aortic lymph nodes according to the inferior mesenteric artery. However, para-aortic lymph nodes from some patients were sent en bloc to pathology without dividing into low and high nodes.
Results	
Prevalence of malignant disease in pelvic and para-aortic lymph nodes	Lymph node metastasis in patients with pelvic and para-aortic lymphadenectomy: 17/69 (24.6%) - from para-aortic and pelvic areas 9/69 (13.0%) - from only the pelvic area: 5/69 (7.2%) - from only the para-aortic area: 8/69 (11.6%) “On multivariate analysis, grade 3 tumour (odds ratio [OR], 5.42; 95% confidence interval [CI], 1.51-19.52; p=0.01) and positive cytology (OR, 4.22; 95% CI, 1.12-15.96; p=0.03) were independent predictors for lymph node metastasis.”
Limitations and other comments	
Limitations	Relatively small total lymph node count retrieved which may have resulted in underestimation of the incidence of nodal metastasis. Risk of selection bias due to retrospective study design. The lack of accurate para-aortic lymph node mapping could lead to the potential overestimation or underestimation of para-aortic lymph node metastasis.

Table 51 – Evidence table (2): lymphadenectomy**Systematic para-aortic and pelvic lymphadenectomy in early stage epithelial ovarian cancer: a prospective study; Ditto 2012⁴⁰³**

Methods	
Design	Prospective study
Source of funding and competing interest	Source of funding: none reported Authors report no potential conflict of interest relevant to this article
Setting	Single centre: IRCCS National Cancer Institute, Milan, Italy
Sample size	Sample size calculated: n=128; n=124 recruited, n=111 analysed



Systematic para-aortic and pelvic lymphadenectomy in early stage epithelial ovarian cancer: a prospective study; Ditto 2012⁴⁰³

Duration and follow-up	Recruitment between January 2003 and January 2011
Statistical analysis	Pearson's chi-square analysis and Fisher's exact test, were used to correlate patient lymph node status and possible risk factors. $P < 0.05$ was considered to be significant. Multivariate logistic regression models were fit by a conditional backward elimination method to identify factors independently associated with nodal involvement and to calculate risk ratios. A p-value criterion of <0.05 was set for variables to be included in the model.
Patient characteristics	
Eligibility criteria	Patients with apparent early epithelial ovarian cancer (FIGO stage I–II) undergoing total surgery with the aim of eradicating the primary malignancy
Exclusion criteria	Extrapelvic metastatic disease, tumours of low malignant potential, and previous retroperitoneal surgery
Patient & disease characteristics	<p>Median age (range): 50 yrs (21–76)</p> <p>Gravida: no: 26 (23.4%); any: 75 (76.6%)</p> <p>Menopausal status: premenopausal: 53 (47.7%), postmenopausal: 58 (52.3%)</p> <p>Preoperative CA125 ≤ 35 U/ml: 31 (27.9%); >35 U/ml: 62 (55.8%); NA: 18 (16.2%)</p> <p>Clinical apparent FIGO stage: IA: 42 (37.8%); IB: 5 (4.5%); IC: 37 (33.3%); IIA: 9 (8.1%); IIB: 13 (11.7%); IIC: 5 (4.5%)</p> <p>Pathological FIGO stage: IA: 40 (36.0%); IB: 3 (2.7%); IC: 31 (27.9%); IIA: 6 (5.4%); IIB: 12 (10.8%); IIC: 4 (3.6%); IIIC: 15 (13.5%)</p> <p>Histological type: mucinous: 15 (13.5%); serous: 25 (22.5%); endometrioid: 38 (34.2%); clear cell: 9 (8.1%); mixed histology: 15 (13.5%); undifferentiated 9 (8.1%)</p> <p>Tumour grade: grade 1: 25 (22.5%); grade 2: 34 (30.6%); grade 3: 52 (46.8%)</p>
Interventions	
Surgical procedures	<p>Bilateral salpingo-oophorectomy and hysterectomy (if not previously performed); washing; random multiple peritoneal biopsies; omentectomy; and systematic pelvic and para-aortic lymphadenectomy.</p> <p>A laparoscopic conservative surgical approach consisted of unilateral salpingo-oophorectomy and complete staging and systematic bilateral pelvic and para-aortic lymphadenectomy.</p> <p>Mean number of removed pelvic nodes \pm SD: 24.8 ± 12.6</p> <p>Mean number of removed \pm SD: 21.5 ± 9.5</p>
Outcome assessment	Pathology information included tumour histology, grade, and stage at diagnosis, number of regional lymph nodes examined, and number of metastatic lymph nodes removed, as well as documented extension away from the primary site.

**Systematic para-aortic and pelvic lymphadenectomy in early stage epithelial ovarian cancer: a prospective study; Ditto 2012⁴⁰³****Results****Prevalence of malignant disease in pelvic and para-aortic lymph nodes**

Lymph node metastasis in patients with pelvic and para-aortic lymphadenectomy: 15/111 (13.5%)

- from para-aortic and pelvic areas 5/111 (4.5%)
- from only the pelvic area: 2/111 (1.8%)
- from only the para-aortic area: 8/111 (7.2%)

Patients with node metastases by histological type

Mucinous: 0/15 (0%)

Serous: 7/25 (28%)

Endometrioid: 4/38 (10.5%)

Clear cell: 0/9 (0%)

Mixed histology: 1/15 (6.7%)

Undifferentiated: 3/9 (33.3%)

“At univariate analysis age, menopause, FIGO stage, grading (G1–2 vs. G3), histological type (serous vs. mucinous vs. other), and bilaterality of the specimens were significant factors for lymph node metastases, while CA125 of >35 U/ml and positive cytology were not. At multivariate analysis, only bilaterality ($p = 0.018$) and menopause ($p = 0.032$) maintained a statistically significant association with lymph node metastases, while the grading lost its significance at the final step of logistic regression analysis.”

“On the basis of the present series and the data in the literature, omitting a systematic lymphadenectomy can be considered for grade I cancers and for mucinous tumours regardless of grade. The rate of positive lymph nodes in the study was 13.5%, with a 95% confidence interval of 7.1–19.9.[...] the logistic regression model presented a good discriminating power measured by the area under the receiver operating characteristic curve of 0.81. This means that the surgeon, using only data on menopausal status and bilaterality of the tumour, has a 19% chance of making the wrong decision regarding the necessity of lymph node dissection.”

Limitations and other comments**Limitations**

Small number of patients enrolled, which probably hampers significance at multivariate analysis for the variables histological subtype grading.

**Table 52 – Evidence table (3): lymphadenectomy**Frequency and distribution of lymph node metastases in epithelial ovarian cancer - significance of serous histology; Haller 2011⁷⁶

Methods	
Design	Retrospective review of the medical records
Source of funding and competing interest	Not reported
Setting	Single centre (tertiary care academic hospital); Department of Obstetrics and Gynecology, Clinical Hospital Centre of Rijeka and Department of Pathology, School of Medicine, University of Rijeka, Rijeka, Croatia.
Sample size	N=173 included
Duration and follow-up	Medical records from January 1995 to December 2007 were retrospectively reviewed
Statistical analysis	“The results are expressed as means, SDs, minimums, maximums, and percentages. Statistical significance was calculated using χ^2 analysis (to determine the relationship between lymph node status and other disease variables) and the independent sample t test (to compare the means). Regression model (Enter method) was applied where appropriate to identify the independent prognostic factor. P values less than 0.05 were considered statistically significant.”
Patient characteristics	
Eligibility criteria	Patients primary epithelial ovarian cancer with complete pelvic and aortic lymphadenectomy up to the level of the left renal vein at first surgery
Exclusion criteria	Borderline tumours including micropapillary serous carcinoma, carcinosarcoma (malignant müllerian mixed tumours), and primary extra-ovarial (peritoneal) carcinomas
Patient & disease characteristics	<p>Mean age (range): 53 yrs (31-74)</p> <p>Patients with serous tumour (n=76, 43.9%) vs. nonserous tumour (n=97, 56.1%):</p> <p>Age \leq 49 yrs: 27 (43.6%) vs. 35 (56.4%); age 50-59 yrs: 24 (42.1%) vs. 33 (57.9%); age \geq 60 yrs: 25 (46.3%) vs. 29 (53.7%);</p> <p>Intraperitoneal stage: pT1: 7 (9.2%) vs. 58 (59.8%); pT2: 15 (19.7%) vs. 20 (20.6%); pT3: 54 (71.1%) vs. 19 (19.6%);</p> <p>Grade 1: 8 (10.5%) vs. 27 (27.8%); grade 2: 37 (48.7%) vs. 30 (30.9%); grade 3: 31 (40.8%) vs. 40 (41.3%);</p> <p>Residual tumour 0 cm: 40 (52.6%) vs. 90 (92.8%); residual tumour <1 cm: 23 (30.3%) vs. 5 (5.2%); residual tumour \geq 1 cm: 13 (17.1%) vs. 2 (2.0%).</p>

**Frequency and distribution of lymph node metastases in epithelial ovarian cancer - significance of serous histology; Haller 2011⁷⁶**

Statistically significant differences between serous and non-serous tumours for intraperitoneal stage, grade and residual tumour size.

Interventions**Surgical procedures**

Lymphadenectomy was a part of primary surgical evaluation, in cases where ovarian malignant lesions are encountered as determined by frozen histological sections. Additional criteria for lymphadenectomy include age younger than 70 years, relatively good medical condition, and intraoperative reduction of tumour to less than 2 cm. After the year 2000, this value was diminished to less than 1 cm. In these patients, lymphadenectomy was associated with hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, multiple peritoneal biopsies, as well as cytoreductive techniques such as supracolic omentectomy, bowel or splenic resection, pelvic, and/or hemidiaphragmatic deperitonization or other procedures, depending on intra-abdominal spread of the disease.

Lymphadenectomy was a part of primary surgery via transperitoneal approach. A pubic-xiphoid incision was made to expose intra-abdominal organs. After the diagnosis was established on the frozen section during surgery in the pelvis, pelvic lymphadenectomy was performed. Aortic lymphadenectomy was the last surgical procedure, performed after completion of intraperitoneal surgery.

Median number (range) of lymph nodes removed per patient: 37 (12-69); pelvic and para-aortic region: 25 (9-47) and 12 (4-40), respectively.

Outcome assessment

All dissected lymph nodes were histologically evaluated on paraffin-embedded and hematoxylin and eosin-stained sections.

Results**Prevalence of malignant disease in pelvic and para-aortic lymph nodes**

Lymph node metastasis in patients with pelvic and para-aortic lymphadenectomy: 59/173 (34.1%)

Age

≤ 49 yrs: 21/62 (33.9%)

age 50-59 yrs: 16/57 (28.1%)

age ≥ 60 yrs: 22/54 (40.7%)

Intraperitoneal stage

pT1: 4/65 (6.2%)

pT2: 10/35 (28.6%)

pT3: 45/73 (61.6%)

Grade

grade1: 6/35 (17.1%)

Frequency and distribution of lymph node metastases in epithelial ovarian cancer - significance of serous histology; Haller 2011⁷⁶

grade 2: 23/67 (34.3%)

grade 3: 30/71 (42.3%)

Residual tumour

0 cm: 28/130 (21.5%)

<1 cm: 17/28 (60.7%)

≥1 cm: 14/15 (93.3%)

Serous vs. nonserous tumours*

Positive lymph nodes: 45/76 (59.2%) vs. 14/97 (14.4%), $p < 0.0001$

Age

≤ 49 yrs: 18/27 (66.7%) vs. 3/35 (8.6%), $p < 0.0001$

age 50-59 yrs: 10/24 (41.7%) vs. 6/33 (18.2%), $p = 0.099$

age ≥60 yrs: 17/25 (68.0%) vs. 5/29 (17.2%), $p = 0.0005$

Intraperitoneal stage

pT1: 2/7 (28.6%) vs. 2/58 (3.4%), $p = 0.075$

pT2: 5/15 (33.3%) vs. 5/20 (25.0%), $p = 0.871$

pT3: 38/54 (70.4%) vs. 7/19 (36.8%), $p = 0.021$

Grade

grade1: 5/8 (62.5%) vs. 1/27 (3.7%), $p = 0.0008$

grade 2: 21/37 (56.8%) vs. 2/30 (6.7%), $p = 0.0001$

grade 3: 19/31 (61.3%) vs. 11/40 (27.5%); $p = 0.009$

Residual tumour

0 cm: 17/40 (42.5%) vs. 11/90 (12.2%), $p = 0.0003$

<1 cm: 15/23 (65.2%) vs. 2/5 (40.0%), $p = 0.588$

≥1 cm: 13/13 (100.0%) 1/2 (50.0%), $p = 0.264$

** we adapted some percentages in comparison serous vs. nonserous tumours as the percentages reported by the authors seem incorrect (age in nonserous group, intraperitoneal stage in nonserous group, grade 1 in serous group).*

**Frequency and distribution of lymph node metastases in epithelial ovarian cancer - significance of serous histology; Haller 2011⁷⁶**

“Logistic regression (Enter method) identified the following independent variables predicting lymph node metastases among the ovarian carcinoma: serous histology ($P = 0.009$; 95% confidence interval [CI], 0.13-0.75), residual tumour mass ($P = 0.0107$; 95% CI, 1.21-4.52), and intraperitoneal stage ($P = 0.0096$; 95% CI, 1.08-4.12), whereas age and tumour differentiation had no prognostic value.”

Limitations and other comments**Limitations**

Indication for lymphadenectomy changed after the year 2000: “Additional criteria for lymphadenectomy include age younger than 70 years, relatively good medical condition, and intraoperative reduction of tumour to less than 2 cm. After the year 2000, this value was diminished to less than 1 cm.”

Table 53 – Evidence table (4): lymphadenectomy

Prognostic value of lymph node involvement in ovarian serous borderline tumours (Study 1); Lesieur 2011⁴⁰⁴

Methods

Design Retrospective review of medical records

Source of funding and competing interest Not reported

Setting Single centre: Departments of Gynecologic Surgery, Pathology and Oncology, Institut Gustave Roussy, France

Sample size N = 49 included

Duration and follow-up Patient enrolment from January 1973 to February 2006

Statistical analysis NA

Patient characteristics

Eligibility criteria Patients who had undergone a lymphadenectomy and had a final diagnosis of a borderline tumour of the ovary (BOT). BOT was defined as an ovarian tumour with the following: (1) a stratified epithelial lining; (2) the formation of microscopic papillary projections; (3) nuclear atypia; and (4) above all, the absence of frank stromal invasion.

Exclusion criteria Not specified

Patient & disease characteristics Mean age: 36.6 y
Infertility: 16.7%



Prognostic value of lymph node involvement in ovarian serous borderline tumours (Study 1); Lesieur 2011⁴⁰⁴

Ovulation induction: 7.5%

Median CA125: 257

Interventions

Surgical procedures

44 patients (89.8%) had undergone radical surgery (bilateral salpingo-oophorectomy with or without hysterectomy) and 5 patients (10.2%) had undergone conservative surgery (conservation of uterus and salvaging at least a portion of 1 ovary).

45 patients (91.8%) had undergone removal of pelvic lymph nodes (PN), 29 (59.2%) removal of para-aortic nodes (PAN): 20 patients had undergone resection of PN alone, 25 had PN plus PAN surgery, and 4 patients had PAN surgery alone.

Patients had undergone either an open or laparoscopic approach performed either during a 1-step surgical procedure, if the diagnosis of BOT was made at a frozen section analysis during the operation, or during restaging surgery. Lymphadenectomy, although not recommended, could have been performed because of enlarged nodes or misdiagnosis of invasive carcinoma.

Outcome assessment

Histological slides were reviewed by one pathologist, tumour stage was recorded using macroscopic description during the surgical procedure and reviewing the pathology records.

Results

Prevalence of malignant disease in pelvic and para-aortic lymph nodes

Lymph node metastasis in patients with pelvic and/or para-aortic lymphadenectomy: 14/49 (28.6%)

Patients with lymph node involvement (n=14, 28.6%) vs. lymph nodes not involved (n=35, 71.4%):

Mean age (yrs): 35.6 vs 37.0

Infertility: 1/13 (7.6%) vs 6/29 (20.7%)

Ovulation induction: 1/13 (7.6%) vs 2/27 (7.4%)

Median CA125: 417.5 vs 179

Limitations and other comments

Limitations

The series from the Institute Gustave Roussy (IGR) concerned 14 cases of lymph node metastases from BOTs accounting for 28.6% of patients with serous advanced-stage BOT. Although this series is limited, this is 1 of the largest ever published. Most of the patients in this series had FIGO stage III or IV disease. The study did not specify the type of lymph node involvement.

One of the main limitations is that the mean number of nodes examined was higher in patients with lymph node involvement with a higher rate of para-aortic lymph node sampling.

**Table 54 – Evidence table (5): lymphadenectomy**

Prognostic value of lymph node involvement in ovarian serous borderline tumours (Study 2); Lesieur 2011 ⁴⁰⁴	
Methods	
Design	Retrospective review of population based registry
Source of funding and competing interest	Not reported
Setting	SEER Program, with data on cancer incidence and survival from 15 population-based cancer registries that cover one quarter of the US population
Sample size	N = 6017 included, N=1503 with lymph node sampling
Duration and follow-up	Data collection between 1973 and 2004. Patients with lymph node involvement had been diagnosed between 1988 and 2000.
Statistical analysis	NA
Patient characteristics	
Eligibility criteria	Patients with BOT, including ICD codes 8442 (serous cystadenoma of borderline malignancy), 8451 (papillary cystadenoma of borderline malignancy), 8462 (serous papillary cystic tumour of borderline malignancy), 8472 (mucinous cystic tumour of borderline malignancy), and 8473 (papillary mucinous cystadenoma of borderline malignancy). Staging of BOT was based exclusively on histologically diagnosed extra-ovarian lesions. Only histopathologically diagnosed tumours that represented either the only primary tumour or the first primary tumour diagnosed for each patient were included.
Exclusion criteria	Not specified
Patient & disease characteristics	<p>Mean age: 48.1 years</p> <p>FIGO stage: I: 4943 (82.2%); II: 351 (5.8%); III: 494 (8.2%); IV: 121 (2.0%); not available: 108 (1.8%)</p> <p>Pathology: serous cystadenoma 1458 (24.2%); papillary cystadenoma: 103 (1.7%); serous papillary cystadenoma: 2240 (37.2%); mucinous cystadenoma: 2076 (34.5%); mucinous papillary cystadenoma: 140 (2.3%)</p> <p>Patients with lymph node sampling (n=1503) vs. no lymph node sampling (n=4514)</p> <p>Mean age: 47.8y vs 48.2y</p> <p>Age <40y: 511 (34.0%) vs. 1669 (37.0%); age 40-60y: 672 (44.7%) vs. 1715 (38.0%); age>60y: 320 (21.3%) vs. 1130 (25.0%)</p> <p>FIGO stage: I: 1104 (73.5%) vs. 3839 (85.0%); II: 144 (9.6%) vs. 207 (4.6%); III: 204 (13.6%) vs. 290 (6.4%); IV: 37 (2.5%) vs. 84 (1.9%); not available: 14 (0.9%) vs. 94 (2.1%)</p>

**Prognostic value of lymph node involvement in ovarian serous borderline tumours (Study 2); Lesieur 2011⁴⁰⁴**

Pathology: serous cystadenoma 375 (25.0%) vs. 1083 (24.0%); papillary cystadenoma: 20 (1.3%) vs. 83 (1.8%); serous papillary cystadenoma: 672 (44.7%) vs. 1568 (34.7%); mucinous cystadenoma: 414 (27.5%) vs. 1662 (36.8%); mucinous papillary cystadenoma: 22 (1.5%) vs. 118 (2.6%)

Statistically significant difference between groups regarding age distribution, FIGO stage and pathology

Interventions**Surgical procedures**

In SEER database documented lymph node removal. Information about the type of lymph node removed (ie, pelvic and/or para-aortic) was not available among the database items. Number of nodes examined (range): 13.3 (1-59) vs 10.52 (1-77)

Outcome assessment

Data from the SEER database, pathology cannot be verified.

Results**Prevalence of malignant disease in pelvic and para-aortic lymph nodes**

Lymph node metastasis in patients with pelvic and para-aortic lymphadenectomy: 93/1496 (6.2%) (7 missings)

Age:

< 40y: 53/509 (10.4%)

40-60y: 28/670 (4.2%)

>60y: 12/317 (3.8%)

FIGO stage:

I: 17/1101 (1.5%)

II: 8/144 (5.6%)

III: 50/200 (25.0%)

IV: 17/37 (46.0%)

Not available: 1/14 (7.1%)

Pathology:

Serous cystadenoma: 29/374 (7.8%)

Papillary cystadenoma: 3/20 (15.0%)

Serous papillary cystadenoma 56/667 (8.4%)

Mucinous cystadenoma: 4/413 (1.0%)



Prognostic value of lymph node involvement in ovarian serous borderline tumours (Study 2); Lesieur 2011⁴⁰⁴

Mucinous papillary cystadenoma: 1/22 (4.5%)

Limitations and other comments

Limitations

Use of the SEER database has limitations: histology cannot be verified and the analysis of the type of surgery performed is too complex because of the multiplicity and vagueness of the headings concerning the surgical procedures and changes in codes over time. Many interesting details were not included: micropapillary pattern and presence of peritoneal or lymph node endosalpingiosis. Another main limitation of the database was the potential unreliability of the staging because some patients reported with lymph node involvement were not classified as having stage III or IV disease (as they should have been).

Table 55 – Evidence table (6): lymphadenectomy

Clinical impact of systematic pelvic and para-aortic lymphadenectomy for pT1 and pT2 ovarian cancer: a retrospective survey by the Sankai Gynecology Study Group; Oshita (2013)³⁶²

Methods

Design	Retrospective review of the medical records
Source of funding and competing interest	Source of funding: none reported Authors report no potential conflict of interest relevant to this article
Setting	Multicentre, 16 institutions belonging to the Sankai Gynecology Study Group, Japan
Sample size	N = 422 included, N=284 with systematic pelvic and para-aortic lymphadenectomy
Duration	Patient enrolment between 1995 and 2005
Statistical analysis	Clinical and pathological characteristics were compared between the patients with and without systematic lymphadenectomy and between patients with and without lymph node metastasis. Correlation of variables was assessed with Fisher's exact, chi-squared, and unpaired t tests.

Patient characteristics

Eligibility criteria	Patients with pT1 and pT2 epithelial ovarian cancer.
Exclusion criteria	Patients who (1) underwent lymphadenectomy only in the pelvic region (2) underwent lymph node sampling or (3) had missing details regarding surgery or pathological assessment.
Patient & disease characteristics	Patients with systematic lymphadenectomy (n=284) vs no lymphadenectomy (n=138) Mean age (range): 53.5 yrs (17-80) vs 52 yrs (16-91)

**Clinical impact of systematic pelvic and para-aortic lymphadenectomy for pT1 and pT2 ovarian cancer: a retrospective survey by the Sankai Gynecology Study Group; Oshita (2013)³⁶²**

Histology: serous: 63 (22.2%) vs 22 (15.9%); endometrial: 71 (25.0%) vs 23 (16.7%); clear cell: 83 (29.2%) vs 32 (23.2%); mucinous: 54 (19.0%) vs 50 (36.2%)*; other: 13 (4.6%) vs 11 (8.0%)

Stage: pT1a: 62 (21.8%) vs 47 (34.1%)*; pT1b: 9 (3.2%) vs 2 (1.5%); pT1c: 133 (46.8%) vs 68 (49.3%); pT2a: 9 (3.2%) vs 0 (0.0%); pT2b: 11 (3.9%) vs 3 (2.2%); pT2c: 60 (21.1%) vs 18 (13.0%)

* The rates of mucinous histology and cases staged at pT1a were significantly higher in the group without systematic lymphadenectomy.

Interventions

Surgical procedures	Systematic lymphadenectomy meant lymph node dissection extending from pelvic lymph nodes to the para-aortic lymph nodes at the height of the renal veins. The median number of resected lymph nodes was 34 (10th–90th percentile: 20–52), consisting of 22 (10th–90th percentile: 12–40) in pelvic lesion and 10 (10th–90th percentile: 3–25) in para-aortic lesion.
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Outcome assessment

Not reported.

Results

Prevalence of malignant disease in pelvic and para-aortic lymph nodes	Lymph node metastasis in patients with pelvic and para-aortic lymphadenectomy: 23/284 (8.1%) - from para-aortic and pelvic areas 9/284 (3.2%) - from only the pelvic area: 2/284 (0.7%) - from only the para-aortic area: 10/284 (3.5%) <i>(numbers don't add up: 21 instead of 23 were subdivided into anatomical region)</i>
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Stage:

pT1: 9/204 (4.4%)

pT2: 14/80 (17.5%)*

Histology:

Serous: 10/63 (15.9%)*

Endometrial: 5/71 (7.0%)

Clear cell: 6/83 (7.2%)

Mucinous: 2/54 (3.7%)



Clinical impact of systematic pelvic and para-aortic lymphadenectomy for pT1 and pT2 ovarian cancer: a retrospective survey by the Sankai Gynecology Study Group; Oshita (2013)³⁶²

Other: 0/13 (0.0%)

* The rate of lymph node metastasis in pT2 was significantly higher than in pT1 and serous adenocarcinoma was also associated with a higher incidence of lymph node metastasis than other histological subtypes.

Limitations and other comments

Limitations

Difference in age distribution between the groups with and without lymphadenectomy: younger patients (under 30 years old) and older patients (over 70 years old) received lymphadenectomy less frequently.

Whether systematic pelvic and para-aortic lymphadenectomy was performed completely or not depended on the patient's background rather than the treatment strategy of each surgeon. The quality of the lymphadenectomies may vary in a multi-institutional study. The extent of a systematic lymphadenectomy may be slightly different depending on the gynaecologist who performed the surgery. Moreover, it is very difficult to evaluate each lymphadenectomy from medical records.

Table 56 – Evidence table (7): lymphadenectomy

Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: Implications for surgical staging; Powless 2011⁴⁰⁵

Methods

Design

Retrospective review of medical records

Source of funding and competing interest

Source of funding: none reported

Authors report no potential conflict of interest relevant to this article

Setting

Single centre, Mayo Clinic, USA

Sample size

N=190 included, 115 with systematic (comprehensive), bilateral pelvic and para-aortic lymph node assessment

Duration

Patient enrolment between January 1994 and December 2003

Statistical analysis

Pearson's Chi-squared analysis and Fisher's Exact Test when needed were used to estimate the differences between patients' lymph node status in terms of evaluated variables. A p-value of <0.05 was considered to be significant. Multivariate logistic regression models were fit, using stepwise selection, to identify factors independently associated with nodal involvement and to calculate risk ratios. A p-value criterion of <0.05 was set for variables to be included in the model.

**Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: Implications for surgical staging; Powless 2011⁴⁰⁵****Patient characteristics**

Eligibility criteria	All cases of apparent early stage epithelial ovarian cancer that was grossly confined to the pelvis at the time of initial exploration without visible evidence of abdominal spread. Patients all underwent surgical lymph node assessment (not all comprehensive).
Exclusion criteria	Patients were excluded if they had undergone neoadjuvant treatment, had synchronous malignancies, or were found to not have epithelial ovarian cancer.
Patient & disease characteristics	Total: n=190 Median age (range): 55 yrs (21-91) Final assigned stage: IA: 54 (28.4%); IB: 10 (5.3%); IC: 51 (26.8%); IIA: 1 (0.5%); IIB: 4 (2.1%); IIC: 37 (19.5%); IIIA: 8 (4.2%); IIIC: 25 (13.2%) Histology: serous: 43 (22.6%); mucinous: 29 (15.3%); endometrioid: 74 (38.9%); clear cell: 26 (13.7%); other: 18 (9.5%) Grade: 1: 36 (18.9%); 2: 56 (29.5%); 3: 98 (51.6%) Ascites present: 39 (20.5%) Median CA 125 (range): 99 U/ml (7-4335)

Interventions

Surgical procedures	All patients underwent surgery by a gynaecologic oncologist, and staging was performed according to existing practice at the time of surgery. This included total hysterectomy, bilateral adnexectomy, omentectomy, directed biopsies of suspicious peritoneal implants and random biopsies of pelvic and upper abdominal peritoneal surfaces. Frozen section was standardly utilized during the surgical evaluation of biopsies and lymph nodes as per our institutional routine and the information was used for intra-operative decision making. 115 patients (60.5%) underwent systematic bilateral pelvic and para-aortic lymph node assessment, 187 patients (98.4%) underwent any pelvic lymph node assessment (46 of them only ipsilateral), 158 patients (83.2%) underwent any para-aortic lymph node assessment (26 of them only ipsilateral). Mean lymph node counts (SD) were 25.2 ± 14.3 (pelvic) and 10.7 ± 7.7 (para-aortic).
Outcome assessment	Data abstracted from medical records, including patient demographics, tumour histology and grade, operative staging procedures, and intraoperative findings.

Results

Prevalence of malignant disease in pelvic and para-aortic lymph nodes	Lymph node metastasis in patients with any lymph node assessment: 25/190 (13.2%) Lymph node metastasis in patients with comprehensive pelvic and para-aortic lymphadenectomy: 19/115 (16.5%)
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**Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: Implications for surgical staging; Powless 2011⁴⁰⁵**

- from para-aortic and pelvic areas 4/115 (3.5%)
- from only the pelvic area: 5/115 (4.3%)
- from only the para-aortic area: 10/115 (8.7%)

Laterality of adnexal involvement:

Unilateral: 6/73 (8.2%)

Bilateral: 13/42 (30.9%) p=0.002

Cytology:

Negative/not done: 8/70 (11.4%)

Positive: 11/45 (24.4%) p=0.067

Ascites:

Absent: 10/88 (11.4%)

Present: 9/27 (33.3%) p=0.007

Histology:

Serous: 9/30 (30.0%)

Mucinous: 0/16 (0.0%)

Other: 10/66 (15.1%) p=0.030

Grade

grade1: 0/14 (0.0%)

grade 2: 1/36 (2.8%)

grade 3: 18/65 (27.7%) p=0.001

FIGO stage:

IA-IC: 9/73 (12.3%)

**Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: Implications for surgical staging; Powless 2011⁴⁰⁵**

IIA-IIIA: 10/42 (23.8%) $p=0.110$

CA 125:

≤ 35 U/ml: 0/12 (0.0%)

> 35 U/ml: 13/53 (24.5%) $p=0.104$

In a multivariate model the independent risk factors for lymph node metastasis among those with comprehensive pelvic and para-aortic lymph node assessment are bilateral adnexal involvement ($p=0.029$) as compared to unilateral, the presence of ascites ($p=0.027$), and a higher FIGO grade ($p<0.001$).

Limitations and other comments**Limitations**

There is no information on the patients who did not undergo any lymph node sampling.

Thoroughness of lymphadenectomy versus lymph node sampling cannot be accurately inferred retrospectively.

Frozen section was standardly utilized during the surgical evaluation of biopsies and lymph nodes as per our institutional routine and the information was used for intra-operative decision making. This could impact the extent of staging biopsies and lymphadenectomy performed at the surgeon's discretion.

Table 57 – Evidence table (8): lymphadenectomy

Impact of surgical staging in stage I clear cell adenocarcinoma of the ovary; Suzuki 2014⁴⁰⁶

Methods

Design	Retrospective review of medical records
Source of funding and competing interest	Supported in part by Japan Society for the Promotion of Science KAKENHI (grant 25462616). Authors report no conflicts of interest.
Setting	Multicentre: 4 hospitals affiliated to The Jikei University School of Medicine, Tokyo, Japan
Sample size	N=165 of which n=80 staged with optimal staging surgery
Duration	Medical records from 2000 through 2009 were retrospectively reviewed
Statistical analysis	Not applicable

**Impact of surgical staging in stage i clear cell adenocarcinoma of the ovary; Suzuki 2014⁴⁰⁶****Patient characteristics**

Eligibility criteria	Patients with stage I pure-type clear cell adenocarcinoma of the ovary.
Exclusion criteria	Not specified
Patient & disease characteristics	Patients with optimal surgical staging (n=80) vs. with non-optimal surgical staging (n=85) Median age (range): 52 yrs (33-74) vs. 54 (30-99); Age <50 yrs: 32 vs. 31; ≥50 yrs: 48 vs. 54; FIGO stage: 1A: 13 vs. 29; IC1: 43 vs. 43; IC2: 6 vs. 7; IC3: 18 vs. 6;

Statistically significant differences between optimal and non-optimal surgical staging in FIGO stage.

Interventions

Surgical procedures	<p>3 types of the surgical staging categories were defined: optimal (including pelvic and para-aortic lymphadenectomy; n=80), minimal (n=74), and inadequate (n=11). In addition, non-optimal staging surgery was defined as minimal or inadequate staging surgeries.</p> <p>The choice between systematic and selected lymphadenectomy in each patient was determined by the institutional treatment policy in staging surgery for presumed early-stage epithelial ovarian cancer at the time of surgery.</p> <p>The number of lymph nodes that were removed and pathologically examined was not considered for the completion of the lymphadenectomy. Pelvic lymphadenectomy was the removal of the common, external, and internal iliac nodes and the obturator node groups to the level of the inguinal ligament. Para-aortic lymphadenectomy was the removal of node-bearing tissues along aorta and vena cava to the level of the renal veins.</p> <p>Median number (range) of lymph nodes removed per patient: systematic lymphadenectomy: 41 (14-89); selected lymphadenectomy: 11 (1-44).</p>
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Outcome assessment	Surgical staging was assessed according to FIGO (approved by the FIGO Executive Board in October 2012 and published in January 2014).
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Results

Prevalence of malignant disease in pelvic and para-aortic lymph nodes	<p>Lymph node metastases were detected in 5 (5.9%) of 85 patients who underwent complete pelvic and para-aortic lymphadenectomy.</p> <p><i>*Different number of patients undergoing complete pelvic and para-aortic lymphadenectomy reported at results as compared to before: 85 instead of 80. Prevalence of malignancy in lymph nodes: 5/80 (6.3%)</i></p>
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Impact of surgical staging in stage i clear cell adenocarcinoma of the ovary; Suzuki 2014⁴⁰⁶

Limitations and other comments

Limitations No comparison between patients with and without lymph node metastasis.
 “The choice between systematic and selected lymphadenectomy in each patient was determined by the institutional treatment policy in staging surgery for presumed early-stage epithelial ovarian cancer at the time of surgery.”

Table 58 – Evidence table (9): lymphadenectomy

Lymphadenectomy in surgical stage I epithelial ovarian cancer; Svolgaard 2014⁴⁰⁷

Methods

Design	Retrospective review of nationwide registry
Source of funding and competing interest	Source of funding: none reported Authors report no potential conflict of interest relevant to this article
Setting	Nationwide: Danish Gynecological Cancer Database (DGCD) (Denmark)
Sample size	N=627 included
Duration	Patient enrolment between January 2005 and May 2011
Statistical analysis	A two-tailed p-value <0.05 was considered significant.
Patient characteristics	
Eligibility criteria	Women presenting with tumour macroscopically confined to the ovary without visible evidence of abdominal spread at the time of the initial surgical exploration, i.e. surgical stage I.
Exclusion criteria	None
Patient & disease characteristics	Median age: 59 y (range 13-90) Grade 1: n=239 (46.8%); grade 2: n=159 (31.1%), grade 3: n=113 (22.1%) (data for n=511) Histology: serous n=192 (30.6%); mucinous n=131 (20.9%); clear cell n=71 (11.3%); endometrioid n=142 (22.6%); other n=91 (14.7%) Systematic lymphadenectomy (N=216) vs. no lymphadenectomy (N=411) Surgical FIGO stage: Ia: 111 (51.3%) vs 213 (51.8%); Ib: 12 (5.6%) vs 36 (8.8%); Ic: 93 (43.1%) vs 162 (39.4%)

**Lymphadenectomy in surgical stage I epithelial ovarian cancer; Svolgaard 2014⁴⁰⁷****Interventions**

Surgical procedures	Lymphadenectomy: clarifying lymph node status by pelvic resection of the external iliac, internal iliac, obturator and common iliac lymph nodes bilaterally, para-aortic lymph nodes around the aorta and vena cava proximal to the aortic bifurcation.
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Outcome assessment	In DGCD it is mandatory to register if no lymphadenectomy was performed or if pelvic and/or para-aortic lymphadenectomy was performed. As part of the pathology registration it is mandatory for the pathologist to register whether lymph nodes were received and if metastases were found. The number of lymph nodes are not registered. Surgical information was compared with pathology registration, in cases of conflict, the pathologist or gynaecologist was contacted.
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Results

Prevalence of malignant disease in pelvic and para-aortic lymph nodes	<p>Lymph node metastasis in patients with pelvic and para-aortic lymphadenectomy: 13/216 (6.0%)</p> <p>Surgical FIGO stage:</p> <p>Ia: 5/111 (4.5%)</p> <p>Ib: 2/12 (16.7%)</p> <p>Ic: 6/93 (6.5%)</p> <p>“In women with metastases serous carcinomas were found in nine (75%), endometrioid in two (16.7%) and carcinosarcomas in one (8.3%).</p> <p>In women with no metastases the distribution was 59 (30.3%) serous, 29 (14.9%) mucinous, 35 (17.9%) clear cell, 49 (25.1%) endometrioid, 10 (5%) carcinosarcoma and 13 (6.7%) undifferentiated.”</p>
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Limitations and other comments

Limitations	Recommendations have changed over time: Pelvic lymphadenectomy for stage I was introduced in the Danish Gynecological Cancer Group guidelines in 2008. According to the new national recommendation from 2012 it is now mandatory to resect pelvic and para-aortic lymph nodes bilaterally. Before 2012 para-aortic lymph node resection was only mandatory in cases of clinical or radiological suspicion and was only consistently performed by a few gynaecological oncology surgeons.
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**Table 59 – Evidence table (10): lymphadenectomy**Lymph node metastasis in patients with epithelial ovarian cancer macroscopically confined to the ovary: review of a single-institution experience; Ulker 2014⁴⁰⁸

Methods	
Design	Retrospective review of tumour database
Source of funding and competing interest	Source of funding: none reported Authors report no potential conflict of interest relevant to this article
Setting	Single centre, Kanuni Sultan Süleyman Training and Research Hospital, Turkey
Sample size	N=62 included
Duration	Patient enrolment between January 2003 and February 2013
Statistical analysis	Pearson's Chi-squared analysis or Fisher's exact tests were used to analyse the evaluated variables. The results were considered statistically significant if the p value was <0.05.
Patient characteristics	
Eligibility criteria	Patients with clinically apparent stage IA/B/C epithelial ovarian carcinoma who underwent a comprehensive staging procedure including pelvic and para-aortic lymphadenectomy
Exclusion criteria	(1) malignant ovarian germ cell and sex-cord stromal tumours, (2) no comprehensive surgical staging, (3) synchronous gynaecologic tumours, (4) fertility sparing surgery.
Patient & disease characteristics	Total: n=62 Mean age \pm SD: 47.6 \pm 10.1 Histology: serous: 25 (40.3%); mucinous: 23 (37%); endometrioid: 9 (14.5%); clear cell: 5 (8%) FIGO Grade: 1: 17 (27.4%); 2: 31 (50%); 3: 14 (22.5%) FIGO stage (final): IA/B: 27 (43.5%); IC: 18 (29%); IIA: 3 (4.8%); IIC: 1 (1.6%); IIIA: 5 (8.1%); IIIC: 8 (12.9%) (= patients with lymphatic metastasis) CA 125: \leq 35 U/ml: 21 (33.8%); 35-200 U/ml: 25 (40.3%); >200 U/ml: 12 (19.3%) Ascites: 35 (56.4%) Positive cytology: 21 (33.8%)
Interventions	

**Lymph node metastasis in patients with epithelial ovarian cancer macroscopically confined to the ovary: review of a single-institution experience; Ulker 2014⁴⁰⁸****Surgical procedures**

The staging process involved obtaining peritoneal washings for cytology and multiple peritoneal biopsies from both suspicious and normal appearing areas, total abdominal hysterectomy and bilateral salpingo-oophorectomy. After the initial step of the surgery, pelvic and para-aortic lymphadenectomy, appendectomy and total omentectomy were also performed. Specifically, pelvic lymphadenectomy included removal of the common, external, internal and obturator node groups to the level of the inguinal ligament. The para-aortic area was exposed just above the bifurcation of the aorta. Para-aortic lymphadenectomy included removal of node bearing tissues along the aorta and vena cava to the level of the renal veins on both sides. Resected pelvic nodes were subdivided as being right or left sided. However, para-aortic nodes could not be subdivided in this way due to the en bloc resection technique that was applied in the para-aortic region.

Mean lymph node counts \pm SD: 20.2 ± 5.3 (pelvic) and 10.7 ± 2 (para-aortic).

Outcome assessment

Data abstracted from medical records

Results**Prevalence of malignant disease in pelvic and para-aortic lymph nodes**

Lymph node metastasis in patients with pelvic and para-aortic lymphadenectomy: 8/62 (12.9%)
- from para-aortic and pelvic areas 1/62 (1.6%)
- from only the pelvic area: 4/62 (6.5%)
- from only the para-aortic area: 3/62 (4.8%)

Histology:

Serous: 5/25 (20.0%)

Mucinous: 1/23 (4.3%)

Endometrioid: 1/9 (11.1%)

Clear cell: 1/5 (20.0%)

FIGO Grade:

1: 0/17 (0.0%)

2: 2/31 (6.4%)

3: 6/14 (42.9%) $p=0.001$

CA 125:

≤ 35 U/ml: 1/21 (4.8%)



Lymph node metastasis in patients with epithelial ovarian cancer macroscopically confined to the ovary: review of a single-institution experience; Ulker 2014⁴⁰⁸

35-200 U/ml: 3/25 (12.0%)

>200 U/ml: 4/12 (33.3%)

Ascites: 6/35 (17.1%) p=0.24

Positive cytology: 7/21 (33.3%) p=0.001

Limitations and other comments

Limitations

There is no information on the patients who did not undergo a comprehensive surgical staging procedure.
Data abstracted from medical records.

5.4. Adjuvant chemotherapy

Table 60 – Evidence table: SR adjuvant chemotherapy in patients with borderline or (micro-) invasive early-stage ovarian cancer

Interventions for the treatment of borderline ovarian tumours (Review);Faluyi 2010³²

Methods

Design Systematic review

Source of funding and competing interest Department of Health, UK; NHS Cochrane Collaboration programme Grant Scheme CPG-506

Search date January 2009

Searched databases Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. Registers of clinical trials, abstracts of scientific meetings, reference lists of included studies were also searched.

Included study designs RCTs

Number of included studies 7 RCTs

**Interventions for the treatment of borderline ovarian tumours (Review);Faluyi 2010³²**

Statistical analysis For time to event data, HR was used to compare the risk of death or disease recurrence in the treatment group with that in the control group; for dichotomous outcomes, RR was used to compare the risk of adverse events (including death) in the treatment group with that in the control group. Authors did not impute missing outcome data for any outcome. Authors were unable to pool the results of the included trials in meta-analyses as they all compared different interventions.

Patient characteristics

Eligibility criteria Trials that compared different interventions in adult women with borderline ovarian tumours of any histological variant (World Health Organization (WHO) histological diagnostic criteria 2003). These criteria included ovarian epithelial hyperplasia, atypia, mitotic activity and detached cell clusters in the absence of destructive stromal invasion.

Exclusion criteria Trials that included women who did not have a clear histological diagnosis; women with tumours including an invasive component, unless findings for women with borderline ovarian tumours were reported separately. Trials in which a second opinion on the pathological diagnosis was not sought.

Patient & disease characteristics All participants (n=340) in the six trials that addressed different forms of adjuvant therapy were managed in tertiary centres, had a median age of 42 to 48 years at enrolment and had a histologically confirmed diagnosis of borderline ovarian tumour. Most of them were followed up for more than 10 years. For five of the six trials more than 96% of participants had Stage I tumours while one trial recruited women with Stage III tumours exclusively.

The participants (n=32) in the trial that compared different extents of conservative surgery, had bilateral tumours, were younger than 35 years of age, wanted to get pregnant as soon as possible and did not have factors suggestive of a possible endocrine, gynaecological or male partner contribution to infertility. More than 90% of the participants in this trial had Stage I tumours and more than 90% of the participants had tumours with serous histology.

Interventions

Intervention group Adjuvant chemotherapy

Control group No adjuvant chemotherapy

Results

Overall survival Number of deaths
Melphalan vs. no adjuvant treatment (1 RCT; mean follow-up 3 years, range 1 to 7))
0/17 (0%) vs. 0/25 (0%)

Thio-TEPA vs. no adjuvant treatment (1 RCT ; mean follow up 147 months, range 4 to 246)):
6/27 (22%) vs. 2/39 (5%), RR 4.33, 95%CI 0.94 to 19.88, p=0.06


Interventions for the treatment of borderline ovarian tumours (Review);Faluyi 2010³²

	p-value (log-rank) reported by trial authors: 0.03
Disease-free survival	<u>Disease recurrence</u> <i>Melphalan vs. no adjuvant treatment (1 RCT; mean follow-up 3 years, range 1 to 7))</i> 0/17 (0%) vs. 0/25 (0%) <i>Thio-TEPA vs. no adjuvant treatment (1 RCT; mean follow up 147 months, range 4 to 246))</i> 1/27 (4%) vs 0/39 (0%)
Quality of life	Not assessed
Adverse events	<i>Thio-TEPA vs. no adjuvant treatment (1 RCT)</i> Severe septic neutropenia (grade 4): 1/27 (4%) vs. 0/39 (0%) Bone marrow toxicity (grade 3): 1/27 (4%) vs.0/39 (0%)
Limitations and other comments	
Limitations	According to the review authors the included trials were biased towards early stage borderline tumours. They evaluated different interventions and no trial was adequately powered to detect differences in survival, therefore the results were not pooled. Furthermore, adverse effects of treatment and the quality of life of participants were inadequately documented.

Table 61 – Evidence table: SR adjuvant chemotherapy (post-surgery) chemotherapy for invasive early stage ovarian cancer

Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (Review); Winter-Roach 2012¹⁴⁵

Methods	
Design	Systematic review
Source of funding and competing interest	Department of Health, UK
Search date	August 2011
Searched databases	Cochrane Gynaecological Cancer Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE. Reference lists of all relevant papers were searched. Also the related articles feature on PubMed was used to identify possibly relevant articles. In addition, MetaRegister, Physicians Data Query and trial registers were searched.



Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (Review); Winter-Roach 2012¹⁴⁵

Included study designs	RCTs
Number of included studies	5 RCTs
Statistical analysis	Results of studies in a meta-analysis were pooled when clinically similar studies were available. For time-to-event data, HRs were pooled using the generic inverse variance facility. For any dichotomous outcomes (e.g. adverse events, and numbers of patients who relapsed or died, if it was not possible to treat these outcomes as time-to-event data), RRs were pooled. Random effects models were used for all meta-analyses. If it was inappropriate to pool the data because of clinical heterogeneity, a meta-analysis excluding outlying studies was performed.
Patient characteristics	
Eligibility criteria	RCTs that compared adjuvant chemotherapy with no adjuvant chemotherapy or placebo, that included women with early stage (I/IIa) epithelial ovarian cancer staged at laparotomy
Exclusion criteria	Not specified
Patient & disease characteristics	<p>A total of 1277 patients were enrolled with a median follow-up of 46 to 121 months. All five trials included women with FIGO stage I ovarian cancer and one trial included women with FIGO stage II as well. One of the trials was flawed by the inclusion of women with borderline ovarian tumours [27/92 (30%)], although they were evenly distributed between the two study groups.</p> <p>In one of the trials there was a predetermined intention to examine, in a subgroup, the effect of staging adequacy in either trial arm. The adequacy of staging in the other trials has not been specified but is assumed to be adequate rather than optimal.</p> <p>For four of the included trials data on histological subtypes could be retrieved from the original publications (n=1179): serous n=350 (29.7%), mucinous n=234 (19.8%), endometrioid n=277 (23.5%), clear-cell n=181 (15.4%), undifferentiated n=34 (2.9%), other n= 58 (4.9%), missing n=45 (3.8%).</p>
Interventions	
Intervention group	<p>Adjuvant chemotherapy (given within three months following surgery, which removed all visible disease.).</p> <p>Four of the included trials used cisplatin-based chemotherapy, while one used melphalan.</p>
Control group	No adjuvant chemotherapy or placebo
Results	
Overall survival	<p>5-year overall survival (3 studies, n=1006): HR=0.71 (95% CI 0.53 to 0.93)</p> <p>Suboptimal staging (2 studies, n=772): HR=0.63 (95% CI 0.46 to 0.85)</p> <p>Optimal staging (2 studies, n=234): HR=1.22 (95% CI 0.63 to 2.37)</p> <p>Tests for subgroup differences: $\text{Chi}^2 = 3.14$, $\text{df} = 1$ ($P = 0.08$) and $I^2 = 68.1\%$</p>


Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (Review); Winter-Roach 2012¹⁴⁵

	10-year overall survival (2 studies, n=925): HR=0.74 (95% CI 0.58 to 0.95) Low/medium risk patients (1 study, n=219): HR=0.95 (95% CI 0.54 to 1.66) High risk patients (1 study, n=201): HR=0.48 (95% CI 0.32 to 0.72)
Disease-free survival	5-year progression/recurrence/disease free survival (4 studies, n=1170): HR=0.67 (95% CI 0.53 to 0.84) Suboptimal staging (3 studies, n=934): HR=0.64 (95% CI 0.50 to 0.82) Optimal staging (2 studies, n=234): HR=0.67 (95% CI 0.36 to 1.22) Tests for subgroup differences: no differences (P = 0.91; I ² = 0%)
	10-year progression/recurrence/disease free survival (2 studies, n=925): HR=0.67 (95% CI 0.54 to 0.84) Suboptimal staging (1 study, n=448): HR=0.60 (95% CI 0.41 to 0.87) Optimal staging (1 study, n=448): HR=0.73 (95% CI 0.38 to 1.42) Low/medium risk patients (1 study, n=477): HR=0.96 (95% CI 0.50 to 1.38) High risk patients (1 study, n=477): HR=0.52 (95% CI 0.33 to 0.82)
Quality of life	Not assessed by review authors. We checked the full text reports of the included RCTs and none of them presented results for quality of life.
Adverse events	A comparison of the risk of adverse events between adjuvant chemotherapy and no chemotherapy was not possible, since none of the included trials reported adverse events among women who did not receive adjuvant chemotherapy.
Limitations and other comments	
Limitations	Post hoc 'risk' subgroups; post hoc assignment of studies to 'staging' subgroups.

5.5. Laparoscopic surgery in early stage ovarian cancer

5.5.1. Systematic reviews

Table 62 – Evidence table of systematic reviews: laparoscopy for early stage ovarian cancer (1)

Lawrie 2013 ²⁰³	
Methods	
Design	SR

**Lawrie 2013²⁰³**

Source of funding and competing interest	National Institute for Health Research (NIHR), UK Methodological, statistical and editorial support as part of the 10/4001/12 NIHR Cochrane Programme Grant Scheme: Optimising care, diagnosis and treatment pathways to ensure cost effectiveness and best practice in gynaecological cancer: improving evidence for the NHS No Col
Search date	December 2011
Searched databases	Cochrane Gynaecological Cancer Group Trials (CGCRG) Register, CENTRAL, MEDLINE, EMBASE, LILACS, Biological Abstracts and CancerLit; handsearch of relevant journals, reference lists of identified studies and conference abstracts
Included study designs	RCTs
Number of included studies	N=0
Statistical analysis	Not applicable
Patient characteristics	
Eligibility criteria	Women with stage I ovarian cancer defined by FIGO as follows: Stage Ia: unilateral tumours Stage Ib: bilateral tumours Stage Ic: identified tumour spillage, tumour capsular penetration, positive peritoneal cytology
Exclusion criteria	Not specifically stated
Patient & disease characteristics	Not applicable
Interventions	
Intervention group	Surgical staging via laparoscopy
Control group	Surgical staging via laparotomy
Results	
Not applicable	
Limitations and other comments	
Comments	


Table 63 – Evidence table of systematic reviews: laparoscopy for early stage ovarian cancer (2)

Lu 2015 ¹⁹⁸	
Methods	
Design	SR
Source of funding and competing interest	Funding not reported No Col
Search date	March 2014
Searched databases	MEDLINE, Embase, Cochrane Library, China Biology Medicine, Chinese National Knowledge Infrastructure
Included study designs	RCTs or well-designed nonrandomized controlled trials with no confinement on allocation concealment, blinding, or districts
Number of included studies	N=11
Statistical analysis	RevMan version 5.2 I ² statistic to estimate the degree of heterogeneity Dichotomous data presented as relative risks with 95%CI If no heterogeneity was detected, a fixed effects model was used to analyse the data. A random effects model was used if there was any unexplained heterogeneity If a sufficient number of eligible trials (>10 studies) existed, a funnel plot analysis was conducted to assess reporting biases Subgroup analysis to test for differences between results published in English and Chinese
Patient characteristics	
Eligibility criteria	Patients with early stage ovarian cancer
Exclusion criteria	Studies in which laparoscopic surgery was performed for diagnostic biopsy instead of radical treatment
Patient & disease characteristics	235 patients in the laparoscopy group and 356 patients in the laparotomy group Age (range): 41.9-55y vs. 41.5-61y Epithelial cancer (range): 70-100% vs. 68-100% FIGO stage I (range): 73-100% vs. 68-100%
Interventions	
Intervention group	Surgical staging via laparoscopy
Control group	Surgical staging via laparotomy

Lu 2015¹⁹⁸**Results (ranges across studies)**

Operative time	MD -54.0 (95%CI -96.99 to -11.01) to 105.00 (61.5 to 148.5)
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Intraoperative blood loss	MD -7.70 (-9.51 to -5.89) to -0.01 (-0.57 to 0.56)
----------------------------------	--

Pelvic lymphadenectomy number	MD -6.70 (-13.3 to -0.1) to 4.50 (-2.14 to 11.14)
--------------------------------------	---

Para-aortic lymphadenectomy number	MD -2.50 (-5.44 to 0.44) to 5.10 (2.13 to 8.07)
---	---

Time to first postoperative flatus	MD -2.60 (-3.07 to -2.13) to -0.45 (-0.79 to -0.11)
---	---

Intraoperative complications	OR 0.28 (0.01 to 6.10) to 5.43 (0.21 to 140.18)
-------------------------------------	---

Postoperative complications	OR 0.13 (0.02 to 0.80) to 0.69 (0.15 to 3.18)
------------------------------------	---

Hospital stay	MD -9.28 (-10.76 to -7.80) to 0.20 (-3.20 to 3.60)
----------------------	--

Recurrence rate	OR 0.04 (0.01 to 0.38) to 6.29 (0.28 to 140.86)
------------------------	---

Postoperative mortality	OR 0.35 (0.01 to 9.24) to 0.53 (0.07 to 4.01)
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Limitations and other comments

Comments	Invalid meta-analysis: pooling of unadjusted data from observational trials
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*5.5.2. Primary studies***Table 64 – Evidence table: Primary study laparoscopy in early-stage ovarian cancer (1)**Chi 2005⁴⁰⁹**Methods**

Design	Non-randomized comparative study
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Source of funding and competing interest	Not reported
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Setting	Single centre, USA
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Sample size	50 patients (20 laparoscopy, 30 laparotomy)
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Duration and follow-up	October 2000 – March 2003
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Chi 2005⁴⁰⁹**Statistical analysis**

Fisher exact test was used to compare categorical variables.
Continuous variables were compared with the Student t test and the Wilcoxon rank sums test.
All statistical tests were 2 sided.

Patient characteristics**Eligibility criteria**

Patients who underwent (attempt of) comprehensive staging for apparent stage I ovarian or fallopian tube cancer, by laparoscopy or laparotomy between October 2000 and March 2003.

Exclusion criteria

Borderline carcinomas, stromal tumours and germ cell tumours were excluded from the laparotomy arm (they were included in the laparoscopy group if the surgical intent was comprehensive staging).
Patients with macroscopic disease noted at the time of surgery were excluded

Patient & disease characteristics

Mean age 49 +/- 11 years.
No significant differences between groups in terms of mean age, BMI, primary disease site, histologic type, tumour grade.
65% of the 20 patients in the laparoscopy group had previous adnexal surgery without staging procedure and 23% of the laparotomy group.

Interventions**Intervention group**

Comprehensive laparoscopic staging including cytological washings, peritoneal biopsies, omentectomy and nodal dissection)

Control group

Comprehensive staging via open surgery (laparotomy)

Results**Operating time**

321 +/-64 min vs. 276 +/-68 min (p=0.04)

Estimated blood loss

235 +/-138 ml vs 367 +/- 208 ml (p=0.003)

Hospital stay

3.1 +/- 0.7 days vs 5.8 +/- 2.6 days (p<0.001)

Complications

0 (0)% vs 2 (7)% (p=1.00)

Limitations and other comments**Limitations**

Data collected retrospectively.
No case-mix adjustment
Many patients had adnexectomy before staging surgery, effect on pathological stage unknown, no data on oncological outcomes reported.



Table 65 – Evidence table: Primary study laparoscopy in early stage ovarian cancer (2)

Ghezzi 2007 ⁴¹⁰			
Methods			
Design	Non-randomized comparative study		
Source of funding and competing interest	Not reported		
Setting	Single centre, Italy		
Sample size	15 patients in laparoscopy group 19 patients in laparotomy group		
Duration and follow-up	1997-2003 laparotomy group 2003-2006 laparoscopy group		
Statistical analysis	The t-test and the Mann-Whitney U-test were performed to compare continuous parametric and non-parametric variables, respectively. Fisher exact test was used to analyse proportions.		
Patient characteristics			
Eligibility criteria	Consecutive women diagnosed with an apparent stage I ovarian cancer on frozen-section analysis as well as patients who had previous adnexal surgery elsewhere and underwent comprehensive staging by laparoscopy. All histological types were included. Control group: consecutive women having had surgical staging via laparotomy for EOC before 2003, with same eligibility criteria.		
Exclusion criteria	Gross evidence of spread of the disease beyond the ovaries.		
Patient & disease characteristics	No significant differences in demographics and preoperative variables.		
		<u>Laparoscopy</u>	<u>Laparotomy</u>
	Serous	7 (46.7%)	14 (73.7%)
	Mucinous	3 (20.0%)	2 (10.5%)
	Endometrioid	3 (20.0%)	1 (5.2%)
	Other	2 (15%)	0
	Grade 1	0	1
	Grade 2	8 (53.3%)	5 (26.2%)

Ghezzi 2007⁴¹⁰

Grade 3 7 (46.7%) 13 (58.4%)

FIGO stage Ic 6 (40%) 5 (26.2%)

Interventions**Intervention group** Comprehensive stage via laparoscopy**Control group** Comprehensive stage via laparotomy**Results****Intraoperative rupture** Intraoperative rupture occurred in 3 (20%) cases in the laparoscopy group and 2 (10.5%) cases in the laparotomy group (p=0.63).**Operating time** 377 +/- 47min vs 272 +/- 81min (p=0.002)**Estimated blood loss** 250 (50-1000) ml vs 400 (150-1000) ml (p=0.28)**Hospital stay** 3 (2-12) days vs 7 (4-14) days (p=0.001)**Complications** 2 (13.3%) vs 8 (42.1%) (p=0.13)**Adjuvant chemotherapy** 11 (73.3%) vs 13 (68.4%)**Limitations and other comments****Limitations** Non-contemporary cohorts

No case-mix adjustment

Table 66 – Evidence table: Primary study laparoscopy in early stage ovarian cancer (3)Lee 2011⁴¹¹**Methods****Design** Non-randomized comparative study**Source of funding and competing interest** Grants from the Yonsei University Research Fund 2010, Faculty Research Grant of Yonsei University College of Medicine 2009 and National Research Foundation of Korea Grant funded by the Korean Government**Setting** Single centre, South-Korea**Sample size** 26 patients in laparoscopy group and 87 in the laparotomy group**Duration and follow-up** 2005-2010**Statistical analysis** Student t test was used for parametric variables and Mann-Whitney test was used for nonparametric variables

Lee 2011⁴¹¹**Patient characteristics**

Eligibility criteria Newly diagnosed untreated gynaecologic cancers and transferred patients with inadequate staging surgery.

Exclusion criteria Evidence of more advanced disease in preoperative work-up
Prior treatment with pelvic radiotherapy or chemotherapy
No follow-up data available

Patient & disease characteristics No significant differences in demographics and preoperative variables

	Laparoscopy	Laparotomy
Serous	10 (38.5%)	24 (27.6%)
Mucinous	8 (30.8%)	22 (25.3%)
Endometrioid	2 (7.7%)	7 (8.0%)
Clear cell	2 (7.7%)	11 (12.6%)
Squamous	0	7 (8.0%)
Sex cord	2 (7.7%)	14 (16.1%)
Grade 1	6 (23.1%)	25 (28.7%)
Grade 2	8 (30.8%)	13 (14.9%)
Grade 3	7 (26.9%)	21 (24.1%)
Unknown grade	5 (19.2%)	28 (32.2%)
FIGO stage IC	14 (53.8%)	35 (39.1%)

Interventions

Intervention group Laparoscopic staging including total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy, appendectomy, infracolic omentectomy

Control group Same procedures by laparotomy

Results

Intraoperative rupture 0 vs 13 (14.9% (p=0.037))

Operating time 227 +/-105.8 min vs 184.6+/-61.4 min (p=0.016)

Estimated blood loss 230.4+/-183.6 ml vs 474.8+/-329.2 ml (p<0.001)


Lee 2011⁴¹¹

Hospital stay	6.4+/-2.6 days vs 12.4+/-5.5 days (p<0.001)
Recurrence	0 vs 8 (9.2) (p=0.195) (longer FU time in laparotomy group)
DFS	13.3+/-10.2 months vs 25.7+/-15.0 months (p<0.0001)
OS	13.3+/-10.2 months vs 27.7+/-15.4 months (p<0.0001)
Limitations and other comments	
Limitations	No case-mix adjustment

Table 67 – Evidence table: Primary study laparoscopy in early stage ovarian cancer (4)

Park 2008a⁴¹²
Methods

Design	Non-randomized comparative study
Source of funding and competing interest	Not reported
Setting	Single centre, Korea
Sample size	52 patients
Duration and follow-up	2004-2007, follow-up 17 months (range 2-40 months)

Statistical analysis
Patient characteristics

Eligibility criteria	Patients with apparent stage I ovarian or fallopian tube cancer who underwent primary surgery as well as those referred for complete staging after incomplete surgery at another hospital.
Exclusion criteria	Gross metastatic tumour outside the ovaries. Borderline malignant ovarian tumours.
Patient & disease characteristics	No between-group differences in age, BMI, parity, menopause, comorbid medical disease and previous abdominal surgery, primary site, histological type, histological grade, LVSI and final FIGO stage. In both groups, 21% of patients was upstaged after surgery.

Park 2008a⁴¹²**Interventions**

Intervention group Laparoscopic staging procedure including peritoneal leavages, random periotneta biopsies, total hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymph node dissection, infracolic omentectomy and appendectomy.
Ovarian tumours were removed using an endobag.

Control group As for laparoscopy, but a generous midline abdominal incision

Results

Intraoperative rupture 2 (10.5%) vs 4 (12.1%) (p=1.00)
Operating time 220.7 +/- 82.7 min vs 274.7 +/- 63.2 min (p=0.012)
Estimated blood loss 240.0 +/- 228.3ml vs 568.2 +/- 451.7ml (p=0.005)
Hospital stay 8.9 +/- 6.1 days vs 14.5 +/- 5.6 days (p=0.002)
Perioperative complications 2 (10.5%) vs 9 (27.3%) (p=0.290)
Adjuvant chemotherapy 78.9% vs 78.8%

Limitations and other comments

Limitations No adjustment for prognostic factors
Patients with secondary surgery also included.

Table 68 – Evidence table: Primary study laparoscopy in early stage ovarian cancer (5)Park 2008b⁴¹³**Methods**

Design Non-randomized comparative study (retrospective chart review)
Source of funding and competing interest Not reported
Setting Single centre, Korea
Sample size 36 consecutive patients
Duration and follow-up 2001-2006; median follow-up 17 months (range 5-61 months)

Park 2008b⁴¹³

Statistical analysis Survival curves and rates were calculated using the log-rank test. Frequency distributions were compared using Chi-squared and Fisher exact test and mean or median values were compared using Student's t and Mann-Whitney U tests.

Patient characteristics

Eligibility criteria

- 1) epithelial ovarian cancer
- 2) apparent FIGO stage I
- 3) patients who underwent a standard surgical procedure

Exclusion criteria Not stated

Patient & disease characteristics Groups similar in terms of age, body mass index, histologic type and histologic grade. The laparoscopic group contained a greater proportion of patients with a history of previous abdominal surgery ($p=0.013$). The laparoscopy contained 6 patients (31.6%) who were transferred after incomplete surgery, while the laparotomy group contained 15 (88.2%) such transferred patients.

Interventions

Intervention group Standard surgical procedure included total hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymphadenectomy, omentectomy, multiple biopsies of the peritoneum, washings, (appendectomy) via laparoscopy.

Control group As for laparoscopy, via vertical midline incision (pubic symphysis to xyphoid)

Results

Intraoperative rupture No intraoperative iatrogenic ruptures of tumours

Operating time 303.8 \pm 84.9min vs 290.4 \pm 120.8 min ($p=0.706$)

Estimated blood loss 231.2 \pm 117.9ml vs 505.3 \pm 279.8ml ($p=0.001$)

Hospital stay 9.4 \pm 4.1 days vs 14.1 \pm 4.2 days($p=0.002$)

Adjuvant chemotherapy 58.8% vs 89.5%

Postoperative complications 0 vs 4 (21.1%)

Intraoperative complications 2(1108%) vs 1 (5.3%)

Recurrence 2 vs 0 recurrences diagnosed during available follow-up (DFS $p=0.123$)

Limitations and other comments

Limitations No adjustment for prognostic factors



Table 69 – Evidence table: Primary study laparoscopy in early-stage ovarian cancer (6)

Liu 2014 ²⁰⁸	
Methods	
Design	Non-randomized comparative study (retrospective chart review)
Source of funding and competing interest	Not reported
Setting	Single centre, China
Sample size	35 cases in the laparoscopy group, 40 cases in the laparotomy group
Duration and follow-up	March 2002-May 2010, FU 36 to 84 months
Statistical analysis	X ² test was used for categorical data
Patient characteristics	
Eligibility criteria	Early-stage ovarian cancer surgically stage after intraoperative pathologic evaluation
Exclusion criteria	Not specified
Patient & disease characteristics	No significant differences in pathological stage, histological type and degree of differentiation
Interventions	
Intervention group	Staging via laparoscopy, including peritoneal washings, hysterectomy, bilateral salpingo-oophorectomy, (pelvic) lymphadenectomy, omentectomy, appendectomy
Control group	Laparotomy, no further details provided
Results	
Intraoperative rupture	3/35 vs 2/40 cases of intraoperative rupture
Operating time	209.71+/-17.57 min vs 200.50+/-20.62 min (p>0.05)
Estimated blood loss	197.14+/-98.48ml vs 345+/-165.95ml (p>0.05)
Hospital stay	16.29+/-6.20 days vs 21.85+/-4.88 days (p<0.05)
Adjuvant chemotherapy	85.71% vs 90.00% (p>0.05)
Postoperative complications	4/35 (11.43%) vs 5/40(12.50%) (p>0.05)
Recurrence rate	5.71% vs 5.00% (p>0.05)
Median time to recurren	13 vs 14.5 months
Median tumour-free survival time	54.3 months vs 57.2 months


Liu 2014²⁰⁸
3-year survival rate 97.14% vs 97.50% (p>0.05)

5-year survival rate 94.11% vs 96.30% (p>0.05)

Limitations and other comments
Limitations No adjustment for prognostic factors

Table 70 – Evidence table: Primary study laparoscopy in early stage ovarian cancer (7)

Koo 2014²⁰⁷
Methods
Design Non-randomized comparative study (retrospective chart review)

Source of funding and competing interest No potential conflict of interest relevant to this article

Setting Single centre, Korea

Sample size 77 patients, 24 in the laparoscopy group and 53 patients in the laparotomy group.

Duration and follow-up October 2006-December 2012, mean follow-up 31 months

Statistical analysis Continuous variables were compared by using the Student t-test and categorical variables were compared by using the 2-tailed chi-square test; Survival analysis were conducted by using the Kaplan-Meier method and surviving data were censored at the date of last follow-up.

Patient characteristics
Eligibility criteria All patients who underwent comprehensive staging for early-stage ovarian cancer

Exclusion criteria

- Borderline ovarian malignancy
- Advanced ovarian cancer FIGO stage III-IV
- Concurrent malignancy of another organ
- Patients referred from other hospital after staging surgery
- Fertility sparing surgery

Patient & disease characteristics

No significant difference in mean age, parity, BMI, preoperative Ca 125-level, preoperative haemoglobin level or previous surgical history.

Referral for restaging surgery after initial surgical confirmation of ovarian cancer was more common in the laparoscopy group (58.3% vs 17.0%; p<0.001).

**Koo 2014²⁰⁷**

Appendectomy was performed more often in the laparotomy group (81.1% vs 41.7%: $p=0.001$)

The mean tumour size was 7.3cm in the laparoscopy group and 11.2cm in the laparotomy group ($p=0.001$)

Interventions

Intervention group Comprehensive staging via laparoscopy including total hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymph node dissection, omentectomy, peritoneal cytology, multiple biopsies from the entire abdominal peritoneum.

Control group As for laparoscopy, laparotomy via midline longitudinal incision

Results

Intraoperative rupture 13 (54.2%) vs 21 (39.6%) ($p=0.465$)

Operating time 192.9+/-73.5 min vs 224.1+/-85.4 min ($p=0.127$)

Estimated blood loss 697.9+/-396.9 ml vs 972.6+/-827.8 ml ($p=0.127$)

Hospital stay 13.7+/-5.4 days vs 13.1+/-4.1 days ($p=0.594$)

Adjuvant chemotherapy 21 (87.5%) vs 48 (90.6%) ($p=0.480$)

Intraoperative complications 0 vs 3(5.7%) ($p=0.548$)

Postoperative complications Similar between groups

Recurrence rate 2 (8.3%) vs 2 (3.8%) ($p=0.585$)

Disease-free survival 59.3 months (95%CI 51.8-66.7 months) vs 66.3 months (95%CI 62.8-69.9 months) ($p=0.367$)

3-year survival rate 86.1% vs 94.7%

Limitations and other comments

Limitations No case-mix adjustment

5.6. Laparoscopy, PET-CT and MRI to predict end result of cytoreductive surgery**Table 71 – Evidence table: SRs prediction of end result of surgery**

Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer; Rutten 2014

Methods

Design Systematic review

**Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer; Rutten 2014**

Source of funding and competing interest	None known
Search date	February 2013
Searched databases	MEDLINE, EMBASE, CENTRAL, the Cochrane Register of Diagnostic Test Accuracy Studies, MEDION and ISI Web of Science.
Included study designs	Diagnostic test accuracy studies
Number of included studies	N=7 (reporting on six cohorts)
Statistical analysis	Data from each study was summarised in two by two tables of TP, FP, TN, FN and used to calculate sensitivity and specificity. Studies providing insufficient data were used to present data on negative predicting values (NPV). Investigation for heterogeneity among estimates of NPV and estimates of test positivity was performed using Cochran's Q-test.
Patient characteristics	
Eligibility criteria	Studies that evaluated the diagnostic accuracy of laparoscopy to determine the resectability of disease in patients who are suspected of advanced ovarian cancer and planned to receive primary debulking surgery were included. Participants included women suspected of having advanced stage ovarian carcinoma (FIGO stage IIB, IIC, IIIA to C, IV), who were scheduled for primary debulking surgery and did not have contraindications for laparoscopy or laparotomy.
Exclusion criteria	Case-control studies were excluded, exclusion criteria not further specified.
Patient & disease characteristics	A total of 408 patients were included in all studies. Only two studies avoided partial verification bias and provided data to calculate sensitivity and specificity. One of these included 64 patients undergoing surgery for a suspected advanced ovarian or peritoneal cancer, mean age 57.4 years (SD 12.7). The second study included 113 patients suspected of advanced primary ovarian cancer, mean age 59 years (range 39 to 81).
Interventions	
Index test	Additional open diagnostic laparoscopy, performed when a patient was planned for primary debulking surgery after conventional diagnostic work-up. Conventional diagnostic work-up consisted of physical and ultrasound examination, serum CA 125 measurement and/or CT or MRI scan.
Target condition	Ovarian cancer deposits that could not be resected at laparotomy to at least less than 1 cm in diameter.
Reference standard	Laparotomy
Results	
Overall survival	Not addressed



Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer; Rutten 2014

Disease-free survival	Not addressed
Quality of life	Not addressed
Adverse events	Not addressed
Debulking (complete/optimal)	Not addressed
Diagnostic accuracy (sensitivity, specificity, PPV, NPV, FNs, FPs)	<p>“Only two studies avoided partial verification bias and provided data to calculate sensitivity and specificity, which did not justify meta-analysis.”</p> <p><i>Sensitivity:</i></p> <p>0.70 (95% CI 0.57 to 0.82)</p> <p>0.71 (95% CI 0.44 to 0.90)</p> <p><i>Specificity (of both studies):</i></p> <p>1.00 (95%CI 0.90 to 1.00)</p> <p>1.00 (95%CI 0.90 to 1.00)</p> <p>“In these two studies there were no false positives.”</p> <p><i>Negative predictive values (NPV)</i></p> <p>0.75 (95% CI 0.55 to 0.86)</p> <p>0.96 (95% CI 0.56 to 0.99)</p> <p>“Negative predictive values (NPV) ranged from 69% to 96%. Although the studies did report sufficient data to calculate NPVs, we judged these estimates too heterogeneous to meta-analyse.”</p> <p>“Three studies described the development or validation of a prediction model with a clear cut-off for test positivity. Sensitivity and specificity of these prediction models were 0.30 to 0.70 and 0.89 to 1.00, respectively. However, one of these studies suffered from partial verification bias.”</p>



Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer; Rutten 2014

Limitations and comments

Limitations

Source of funding or support was not reported for each of the included studies. Methodological heterogeneity exists on the definition of a positive/negative reference test. Three studies used the cut-off of 1.0 cm for residual disease. Heterogeneity exists between the included studies regarding the pre-treatment work-up, the clinical and/or radiological tests performed, and their influence on study/debulking eligibility. Two of seven original studies avoided partial verification bias by referring all patients to laparotomy (i.e. the reference test). Consequently, of the 168 women considered ineligible for a debulking (i.e. positive at laparoscopy), only 52 cases (52/168=31%) were completely verified. Applicability to our research question: the two original studies which avoided the risk of partial verification bias, included a mix of primary debulking, interval debulking and recurrent disease laparotomies, without clear subanalyses.

Table 72 – Evidence table (1): DTA study prediction of end result of surgery

Espada 2013; Diffusion-weighted magnetic resonance imaging evaluation of intra-abdominal sites of implants to predict likelihood of suboptimal cytoreductive surgery in patients with ovarian carcinoma.

Methods

Design	Prospective DTA study
Source of funding and competing interest	Source of funding not reported Competing interests not disclosed
Setting	Single centre study, Spain
Sample size	N=34
Time interval between tests	Within 15 days
Statistical analysis	“Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for each feature for diffusion-weighted magnetic resonance imaging (DWMRI) predicting affection in exploratory laparotomy (EL); same parameters were calculated for each feature for DWMRI and EL for predicting suboptimal cytoreduction. According to literature, minimum criteria for including a certain anatomical site in the predictive score were: specificity >75%, PPV >50% and NPV >50%. Receiver operating characteristic (ROC) curve analysis was used to assess the ability of the model to predict surgical outcome for DWMRI and EL. Comparison between the areas under ROC curves was performed, using the Hanley and McNeil method. The Fisher exact test was used to examine the strength of statistical association between each predictive score and surgical outcome. Statistical analysis was carried out using the PASW Statistics v. 18.0 software.”



Espada 2013; Diffusion-weighted magnetic resonance imaging evaluation of intra-abdominal sites of implants to predict likelihood of suboptimal cytoreductive surgery in patients with ovarian carcinoma.

Patient characteristics

Eligibility criteria Patients undergoing surgery for a suspected advanced ovarian carcinoma between December 2006 and June 2012.

Patient characteristics N=34
Median age (SD): 53.1 (11.9) years
Disease stage: stage III: 28 (82.4%); stage IV: 6 (17.7%)
Histology: serous adenocarcinoma: 28 (82.4%), endometrioid/clear cell carcinoma: 3 (8.8%), mucinous adenocarcinoma: 2 (5.9%), poorly differentiated carcinoma; 1 (2.9%)

Prevalence of disease Prevalence of residual disease > 1 cm 8/34 (24%)

Interventions

Index test(s) "All patients underwent a preoperative pelvic and abdominal MRI study for tumour staging at a 3-T system (GE Medical System, Milwaukee, WI, USA). A phased-array torso surface coil was used, with parallel imaging with an acceleration factor of 2 in the phase direction and 1 in the slice direction."

Diffusion-weighted magnetic resonance imaging (DWMRI). DWMRI of the pelvis study was acquired in the axial plane using a spinecho echo planar imaging acquisition. DWI parameters included a *b* value of 600 s/mm, TE 2.8, TR 4,800, matrix 128×128, slice thickness 5 mm, interslice gap 0 mm, 6 nex, FOV 38, phase FOV 0.70. DWMRI of the abdomen was also acquired in an axial plane with the same sequence but with a large FOV.

A score was constructed that addressed the affection of 9 sites: (1) small and/or large bowel mesentery, (2) hepatic parenchyma, hylium or surface over 2 cm, (3) omental extension (spleen or splenic hylium, stomach or lesser sac), (4) diaphragm, (5) peritoneal thickening, (6) peritoneal macroscopic implants (≥2 cm), (7) miliar visceral peritoneum implants, (8) massive ascites, (9) suprarenal para-aortic lymph nodes (≥1 cm)

The score with the highest overall accuracy was selected as threshold: score of ≥6 (accuracy 91.1 %)

DWMRI findings were evaluated by the same two radiologists, who were blind to the clinical data.

Reference standard Exploratory laparotomy (EL) "with the aim of performing a maximal tumour cytoreduction to residual disease of 1 cm in maximal diameter"

Patients were operated on by the same gynaecological oncologist who was aware of the DWMRI findings.



Espada 2013; Diffusion-weighted magnetic resonance imaging evaluation of intra-abdominal sites of implants to predict likelihood of suboptimal cytoreductive surgery in patients with ovarian carcinoma.

Results

Debulking (complete/optimal) “Twenty-six patients (76.5 %) were considered as being optimally cytoreduced to residual tumour < 1 cm.”

Diagnostic accuracy (sensitivity, specificity, PPV, NPV, FNs, FPs)

Target condition: residual tumour size >1 cm

Sensitivity: 0.75 (95%-CI 0.35 to 0.97)

Specificity: 0.96 (95%-CI 0.80 to 1.00)

PPV: 0.86 (95%-CI 0.42 to 1.00)

NPV: 0.93 (95%-CI 0.76 to 0.99)

In a hypothetical study of 1000 patients and with a prevalence of 24% (= study prevalence)

60 (95%-CI 7 to 156) patients will be incorrectly classified as being resectable (FNs)

30 (95%-CI 0 to 152) patients will be incorrectly classified as not being resectable (FPs)

Limitations and other comments

Limitations

High risk of bias for the domains Patient selection, Index test and Reference standard

Applicability concerns for the domains Patient selection and Index test

DW-MRI not assessed as add-on test to CT

Very small sample size ((very) wide 95%-CIs)

Confusion about the reference standard: elective laparotomy (EL) seems to be the reference standard, but in Tables 2 and 3 of the report the diagnostic accuracy of EL is also reported. It's not clear with what other reference standard EL is compared.

Table 73 – Evidence table (2): DTA study prediction of end result of surgery

Forstner 1995; Ovarian cancer: staging with CT and MR imaging

Methods

Design Prospective DTA study

Source of funding and competing interest Austrian E. Schroedinger Stipendium (100874- Med)

Competing interests not disclosed

Setting Single centre study, USA



Forstner 1995; Ovarian cancer: staging with CT and MR imaging

Sample size	N=82
Time interval between tests	Within four weeks
Statistical analysis	"Descriptive statistical tests by using the method by Griner et al (1981); χ^2 test of proportions and the two-tailed Fisher exact test for the statistical difference between CT and MR imaging findings ($p=.05$ level of significance); analysis of variance to compare CA-125 levels between the stages and grades (borderline, stage I, stage II, stage III and stage IV)."
Patient characteristics	
Eligibility criteria	"Patients who (between June 1990 and May 1994), on the basis of clinical findings (which included physical examination, sonographic, or laboratory data), were suspected to have ovarian cancer and who were candidates for surgical staging were recruited into the study."
Patient characteristics	<p>N= 82: CT: n= 43; MRI: n= 50 (Note: 11 cases had both CT and MRI)</p> <p>Mean age (range): 52 (17 to 82) years</p> <p>Disease stage based on laparotomy (presented stratified for imaging results; n=93): stage I: 18 (19.4%); stage II: 9 (9.7%); stage III: 64 (68.8%); stage IV: 2 (2.1%)</p> <p>Histology: serous adenocarcinoma: 39 (47.6%), endometrioid/clear cell carcinoma: 9 (11.0%), mucinous adenocarcinoma: 10 (12.2%), undifferentiated carcinoma: 5 (6.1%), malignant mixed mullerian tumour: 2 (2.4%), malignancy in dermoid/endometrial cyst: 4 (4.9%), granulosa cell tumour: 2 (2.4%), dysgerminoma 1 (1.2%), metastasis 1 (1.2%)</p>
Prevalence of disease	Prevalence of "unsuccessful cytoreduction" (definition not provided) CT: 6/43 (14%); MRI: 11/50 (22%)
Interventions	
Index test(s)	<p>Index test assignment: "Patient scheduling was based on a variety of factors, which included scheduling availability, preference of referring physicians or third-party payers, and contraindications to CT (eg, allergy to contrast material) or MR imaging (eg, pacemakers and intracranial vascular clips)."</p> <p>CT: "CT was performed with a GE 9800 CT scanner (GE Medical Systems, Milwaukee, Wis). According to a standardized protocol, dynamic scans were obtained at 7-10-mm increments through the abdomen and pelvis immediately after intravenous administration of 150 mL of contrast material by using a power injector (Medrad, Pittsburgh, Pa) at a rate of 2 mL/sec. The scanning field extended from the dome of the diaphragm to the inguinal region. Contrast material was also administered orally and rectally in each patient. Dynamic scanning through the liver (from the tip to the dome) was started after 40 mL had been injected. Dynamic scanning was performed from the symphysis pubis toward the iliac crest. The area between the pelvis and abdomen was scanned without use of the dynamic protocol."</p>



Forstner 1995; Ovarian cancer: staging with CT and MR imaging

MRI: "MRI performed with a 1.5-T system (Signa; GE Medical Systems). The imaging protocol included T1-weighted, T2-weighted, and contrast-enhanced T1-weighted sequences in the transaxial plane. Transaxial images were obtained from the dome of the liver to the inferior pubic ramus (10.0-mm section thickness with a 2.0-mm intersection gap in the abdomen and 5.0-mm section thickness with a 2.5- or 1.0-mm intersection gap in the pelvis) with T1-weighted (500-600/11-15[repetition time msec/echo time msec]; (n=50), T2-weighted (conventional spinecho technique; 2,000/80; n=12), and fast spin-echo (4,000-5,500/85-102; echo train length of eight; n= 38) techniques. Additional sagittal T2-weighted images were obtained in the pelvis with the imaging parameters described above. Transaxial T1-weighted imaging sequences through the pelvis (imaged first) and abdomen were repeated immediately after intravenous bolus injection of gadopentetate dimeglumine (0.1 mmol/kg; Magnevist; Berlex Laboratories, Wayne, NJ). Other MR imaging parameters were two signals acquired, a 256 x 192 matrix, and a 32- 40-cm field of view for T1-weighted imaging; two signals acquired, a 256 x 192 matrix, and a 32-40-cm field of view for conventional T2-weighted imaging; and four signals acquired, a 256 x 256 matrix, and a 28-40-cm field of view for fast spinecho T2-weighted imaging.

Intramuscular glucagon (1 mg; Eli Lilly, Indianapolis, Ind) was administered in all patients. Administration of glucagon was not medically contraindicated in any patient. A body coil was used in imaging the abdomen (in all patients) and pelvis (n=18). In 32 patients, the pelvis was imaged by using the phased-array coil."

"CT and MR images were analyzed prospectively by two of the authors (R.F., H.H.); discrepancies were resolved in consultation, and interpretations were rendered in concert. In patients who underwent both CT and MR imaging, images were reviewed randomly and a consensus reading was obtained independently for each type of examination."

Reference standard

"Staging laparotomy (total abdominal hysterectomy: all patients); bilateral salpingo-oophorectomy: n=78; and infracolic omentectomy: n=58 or supracolic omentectomy: n=24). In all patients, resection or cytoreduction of peritoneal implants was performed throughout the abdomen and pelvis"

No definition of (un)successful cytoreduction was presented.

Results**Debulking (complete/optimal)**

"Successful cytoreduction was not achieved in six patients who underwent CT and in 11 patients who underwent MR imaging"

**Diagnostic accuracy
(sensitivity, specificity, PPV,
NPV, FNs, FPs)**

Target condition: 'unsuccessful cytoreduction' (definition not provided)
CT
Sensitivity: 0.50 (95%-CI 0.12 to 0.88)
Specificity: 1.00 (95%-CI 0.91 to 1.00)
PPV: 1.00 (95%-CI 0.29 to 1.00)

**Forstner 1995; Ovarian cancer: staging with CT and MR imaging**

NPV: 0.93 (95%-CI 0.80 to 0.98)

In a hypothetical study of 1000 patients and with a prevalence of 18% (= average study prevalence)

90 (95%-CI 22 to 158) patients will be incorrectly classified as 'successful cytoreduction' (FNs)

0 (95%-CI 0 to 74) patients will be incorrectly classified as 'unsuccessful cytoreduction' (FPs)

MRI

Sensitivity: 0.91 (95%-CI 0.59 to 1.00)

Specificity: 0.97 (95%-CI 0.87 to 1.00)

PPV: 0.91 (95%-CI 0.59 to 1.00)

NPV: 0.97 (95%-CI 0.87 to 1.00)

In a hypothetical study of 1000 patients and with a prevalence of 18% (= average study prevalence)

16 (95%-CI 0 to 74) patients will be incorrectly classified as 'successful cytoreduction' (FNs)

25 (95%-CI 0 to 107) patients will be incorrectly classified as 'unsuccessful cytoreduction' (FPs)

**Limitations
comments****and other****Limitations**

Applicability concerns for the domains Patient selection and Index test

Sample also includes stage I and II and non-epithelial carcinomas.

Index test no add-on to CT.

No definition provided for what constitutes "successful cytoreduction".

Change of methodology / design during the study: "Initially, all patients were to be scheduled to undergo both CT and MR imaging examinations. Because of difficulties in patient recruitment, the study design was changed to require either CT or MR imaging."

"In patients who underwent both CT and MR imaging, images were reviewed randomly and a consensus reading was obtained independently for each type of examination."

Assignment of CT or MR imaging examinations occurred in a non-randomized manner (see above; index test paragraph).

Methodology heterogeneity: for MRI, T2w sequence parameters (SE vs. FSE) and the used coil (pelvis vs phased array) were non-uniformly applied.

**Table 74 – Evidence table (3): DTA study prediction of end result of surgery**

Qayyum 2005; Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer	
Methods	
Design	Retrospective DTA study
Source of funding and competing interest	Source of funding not reported Competing interests not disclosed
Setting	Single centre study, USA
Sample size	N=137
Time interval between tests	Within four weeks
Statistical analysis	“Statistical analysis was performed using the two-sided Fisher exact test. P values of less than 0.05 were considered statistically significant.”
Patient characteristics	
Eligibility criteria	Women who underwent primary cytoreductive surgery for epithelial ovarian cancer at our institution over a 9-year period. Seventy women did not undergo preoperative CT or MR imaging and were excluded from the study.
Patient characteristics	N=137 Mean age,(range): 58 (17 to 83) years Stage I/II/III/IV: 26/6/94/11 Histology: epithelial ovarian cancer, not further specified.
Prevalence of disease	Prevalence of residual disease >2 cm: CT 14/91 (15%), MRI 7/46 (15%)
Interventions	
Index test(s)	CT or MRI (CT: n=91; MRI: n=46) CT: “CT was performed with a GE 9800 CT scanner (GE Medical Systems, Milwaukee, WI) (n = 30) or with a GE High Speed Advantage (n = 20). The CT protocol utilized 7–10 mm incremental imaging through the abdomen and pelvis. There was a 70-s delay from onset of intravenous injection of 150 ml of nonionic contrast material using a power injector (Medrad, Pittsburgh, PA) at a rate of 2 ml/s. Oral and rectal contrast materials were also administered. Helical scans were performed with 7-mm collimation and a pitch of 1. Outside CT examinations (n=41) were performed on conventional and helical scanners from several different manufacturers; scans were obtained with both oral and intravenous contrast.”

**Qayyum 2005; Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer**

MRI: "MRI was performed with a 1.5-T system (Signa; General Electric Medical Systems). The protocol included pelvic imaging with precontrast, axial T1-weighted spin-echo sequence (TR/TE, 5-700/10-15; slice thickness/gap, 8/2), axial and sagittal T2-weighted fast-spin-echo sequences (TR/TE, 4000/85; slice thickness/gap, 5/1; echo train length of 8), and axial T1-weighted spin-echo sequence (TR/TE, 5-700/ 10-15; slice thickness/gap, 8/2) after intravenous bolus injection of gadopentetate dimeglumine (0.1 mmol/kg; Magnevist; Berlex Laboratories, Wayne, NJ). Pelvic imaging was followed by imaging of the body with axial T1- weighted spoiled-gradient-echo sequence (TR/TE, 90-150/ 4.2; slice thickness/gap, 8/2, flip angle of 70°) post gadolinium incremental slices to the diaphragm, axial T2 weighted single-shot-fast-spin-echo sequence (TR/TE, maximum/ 100; slice thickness/gap, 8/2), and axial T1-weighted spin-echo sequence (TR/TE, 5-700/10-15; slice thickness/ gap, 8/2) in incremental slices to above the renal hila. A field of view of 24–28 cm was used for the pelvis and 32–40 cm for the abdomen. Intramuscular glucagon (1 mg; Eli Lilly, Indianapolis, IN) was administered to all patients prior to scanning. The outside MR studies (n=8) were performed on 1.5-T scanners from different manufacturers. The pulse sequences varied but studies included at least one gadolinium enhanced series."

"Two experienced radiologists independently analysed all the CT and MR images. Both readers were aware of the diagnosis of ovarian cancer but blinded to the stage and surgical outcome. Specific criteria for inoperable tumour were used to predict suboptimal cytoreduction. The imaging criteria for inoperable tumour were derived from surgical and imaging literature and supplemented by personal communication with experts in gynaecologic oncology. Patients were considered to have inoperable tumour when lesions measuring greater than 2 cm in diameter were located at any one or more of several critical sites"

Reference standard	Surgery (performed by one of three gynaecologic oncology attending surgeons; staging based on the International Federation of Gynaecology and Obstetrics (FIGO) classification)
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"Reduction of all tumour sites to less than 2 cm in maximum diameter was considered optimal."

Results

Debulking (complete/optimal)	Suboptimal (>2 cm) cytoreductive surgery: 21/137 (15%) "Of the 21 patients with suboptimal cytoreduction, 15 had stage III and 6 had stage IV disease." "Overall, optimal cytoreduction was achieved in 100% of cases with stage I (26/26) or stage II (6/6), 84% with stage III (79/94), and 45% with stage IV disease (5/11)."
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Diagnostic accuracy (sensitivity, specificity, PPV, NPV, FNs, FPs)	Target condition: residual tumour size >2 cm CT (n=91) Sensitivity: 0.79 (95%-CI 0.49 to 0.95)
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**Qayyum 2005; Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer**

Specificity: 0.99 (95%-CI 0.93 to 1.00)

PPV: 0.92 (95%-CI 0.62 to 1.00)

NPV: 0.96 (95%-CI 0.89 to 0.99)

In a hypothetical study of 1000 patients and with a prevalence of 15% (= study prevalence)

31 (95%-CI 7 to 76) patients will be incorrectly classified as having no residual tumour (FNs)

8 (95%-CI 0 to 59) patients will be incorrectly classified as having residual disease >2 cm (FPs)

MRI (n=46)

Sensitivity: 0.71 (95%-CI 0.29 to 0.96)

Specificity: 1.00 (95%-CI 0.91 to 1.00)

PPV: 1.00 (95%-CI 0.48 to 1.00)

NPV: 0.95 (95%-CI 0.83 to 0.99)

In a hypothetical study of 1000 patients and with a prevalence of 15% (= study prevalence)

43 (95%-CI 6 to 106) patients will be incorrectly classified as having no residual tumour (FNs)

0 (95%-CI 0 to 76) patients will be incorrectly classified as having residual disease >2 cm (FPs)

“CT and MR imaging were equally effective ($p = 1.0$) in the detection of inoperable tumour.”

Limitations and other comments**Limitations**

High risk of bias for the domain Reference standard

Applicability concerns for all domains

Index test not assessed as add-on test to CT

Target condition was defined as residual disease >2 cm

“The cross-sectional design may have resulted in a selection bias with respect to which patients underwent preoperative imaging. The direction of this bias is difficult to ascertain.”

“Patients underwent either CT or MR imaging. True comparison of the two modalities would involve imaging each patient with both CT and MR imaging.”

**Qayyum 2005; Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer**

"This was a retrospective study and variation in imaging techniques occurred over the accrual period of the study as well as between different imaging centres, necessary for the large patient number, which may have resulted in an underestimation of non-resectability. Referral to our institution for treatment may have led to a selection bias of patients with advanced disease. Patients with all stages of disease were included that would tend to increase the rates of optimal surgical cytoreduction. We did not know which patients had stage I or II disease at the time of imaging, and this is representative of clinical practice."

"Over the long accrual period of the study the criteria for optimal cytoreduction decreased from 2 to 1 cm, but to maintain consistency the 2-cm cut-off was not altered."

Table 75 – Evidence table (4): DTA study prediction of end result of surgery**Shim 2015; Nomogram for predicting incomplete cytoreduction in advanced ovarian cancer patients****Methods**

Design	Prediction study with DTA component
Source of funding and competing interest	Source of funding not reported "The authors have no conflicts of interest or financial ties to disclose"
Setting	Single centre, South Korea
Sample size	N=343
Time interval between tests	Within four weeks
Statistical analysis	"Bivariate relationships between risk factors and incomplete cytoreduction assessed using the model development cohort; predictive values determined using univariate analysis ($p < 0.2$) and tested using bootstrap resampling, in which 1000 repetitions were included in the logistic regression model with backward elimination. Criterion for inclusion in the final logistic model: 50% relative selection frequency. To assess model fit, the concordance index was used to measure discrimination by calculating the area under the receiver operating characteristics curve. The Hosmer–Lemeshow test was used to assess calibration. The model was applied to the validation cohort for external validation. Using the same methods, discrimination and model calibration were tested. Positive likelihood ratio was calculated using the following formula: $\text{Positive likelihood ratio} = \text{sensitivity} / (1 - \text{specificity})$. All analyses were performed using SPSS (version 19.0; SPSS, Chicago, IL) and R version 3.0.0, $p < 0.05$ was considered significant."

Patient characteristics



Shim 2015; Nomogram for predicting incomplete cytoreduction in advanced ovarian cancer patients

Eligibility criteria	Age between 18 and 80 years; pathologically confirmed ovarian cancer; positron-emission tomography/computed tomography performed 4 weeks prior to surgery; primary staging and subsequent cytoreductive surgery; postoperative diagnosis of FIGO stages III–IV cancer. Patient enrolment between 2006 and 2012. Patients who did not receive primary treatment at the indicated institution, received neoadjuvant chemotherapy or had a history of other malignancies were excluded.
Patient characteristics	Model development cohort: n = 240; validation cohort: n = 103 (Total n = 343) Median age, years (range): 55 (27-80) vs. 54 (20-76) FIGO stage, n (%), IIIA/ IIIB/ IIIC/ IV: 6 (2.5)/ 10 (4.2)/ 173 (72.1)/ 51 (21.3) vs. 2 (1.9)/ 4 (3.9)/ 67 (65.0)/ 30 (29.1) Histology, n (%), serous/ mucinous/ endometrioid/ clear cell/ transitional cell/ carcinosarcoma/ others: 185 (77.1)/ 5 (2.1)/ 9 (3.8)/ 19 (7.9)/ 6 (2.5)/ 10 (4.2)/ 6 (2.5) vs. 89 (86.4)/ 0/ 4 (3.9)/ 3 (2.9)/ 4 (3.9)/ 1 (1.0)/ 2 (1.9)
Prevalence of disease	Prevalence of residual disease > 0 cm 223/343 (65%)
Interventions	
Index test(s)	Positron emission tomography/computed tomography (PET/CT) Furosemide (40-mg tablet) and duspatalin (135-mg tablet) were orally administered just before venous blood glucose measurement. Venous blood glucose levels were maintained b140 mg/dl. All patients were injected with 0.2 mCi/kg 18F-fluorodeoxyglucose and allowed to rest in a sitting or supine position for approximately 60 min prior to scanning. The patients were then positioned in the scanner with their arms above their heads. Positron-emission tomography/computed tomography scans from the base of the skull to the mid-thigh were performed using Discovery STE (GE Healthcare, Waukesha, WI), Biograph Truepoint 16 (Siemens/CTI, Knoxville, TN), or Biograph Truepoint 40 (Siemens/CTI) scanners. The scanners obtained combination multislice computed tomography and positron-emission tomography tomographs. The computed tomography data were used for attenuation correction. A total of five to six bed positions for 2–3 min per position were acquired for emission scanning (3 min/bed with the Discovery STE and Biograph Truepoint 16; 2 min/bed with the Biograph Truepoint 40). All scans were reconstructed using an ordered-subsets expectation maximization algorithm (20 subsets and two iterations for the Discovery STE; 16 subsets and two iterations for the Biograph Truepoint 16; 21 subsets and three iterations for the Biograph Truepoint 40). Calibration of each scanner against dose calibrators and well counters was routinely performed. The measured standardized uptake value of the phantom was within the acceptable range of 90–110%. The mean standardized uptake value of the liver was also calculated by drawing a three-dimensional region of interest with a 3-cm diameter within the normal inferior right lobe. Further details with regard to the criteria used to interpret positron-emission tomography scans are described in the Supplemental Methods.



Shim 2015; Nomogram for predicting incomplete cytoreduction in advanced ovarian cancer patients

Reference standard Systematically performed surgical exploration of the abdominal cavity. Complete cytoreduction defined as 'no gross residual tumour' (i.e. residual disease = 0 cm)

Results

Debulking (complete/optimal) "Complete cytoreduction was achieved in 120 patients (35%)."

Diagnostic accuracy (sensitivity, specificity, PPV, NPV, FNs, FPs)

Target condition: residual tumour size > 0 cm

Combined development and validation set:

Sensitivity: 0.66 (95%-CI 0.60 to 0.73)

Specificity: 0.88 (95%-CI 0.80 to 0.93)

PPV: 0.91 (95%-CI 0.85 to 0.95)

NPV: 0.58 (95%-CI 0.51 to 0.66)

In a hypothetical study of 1000 patients and with a prevalence of 65% (= study prevalence)

221 (95%-CI 175 to 260) patients will be incorrectly classified as having no residual tumour (FNs)

42 (95%-CI 24 to 70) patients will be incorrectly classified as having residual disease >0 cm (FPs)

Limitations and other comments

Limitations

Applicability concerns for the domains Index test and Reference standard

Index test no add-on to CT

Index test (predictors summarised in a nomogram) does not solely include PET/CT based determinants, but also a surgical aggressiveness index

PET/CT was not performed in all cases: of all advanced stage patients 77% underwent preoperative PET/CT.

5.7. Aim of cytoreductive surgery: no macroscopic disease?

5.7.1. Prognostic value end result of surgery

Table 76 – Evidence table: SRs prognostic value end result of surgery

Optimal primary surgical treatment for advanced epithelial ovarian cancer; Elattar 2011²⁵⁹

Methods

Design Systematic review

**Optimal primary surgical treatment for advanced epithelial ovarian cancer; Elattar 2011²⁵⁹**

Source of funding and competing interest	Department of Health, UK. NHS Cochrane Collaboration programme Grant Scheme CPG-506 Declaration of interest: none
Search date	August 2010
Searched databases	MEDLINE, EMBASE, CENTRAL, the Cochrane Gynaecological Cancer Review Group Trials Register
Included study designs	Prospective and retrospective cohort studies (including data from RCTs) and unselected case series of 100 or more patients which included concurrent comparison groups. Case-control studies, observational studies that did not have concurrent comparison groups, included fewer than 100 patients or that didn't apply multivariable analyses to correct for baseline differences.
Number of included studies	N=11 (only retrospective studies)
Statistical analysis	Hazard ratios (HRs) were pooled using the generic inverse variance method (random-effect models)
Patient characteristics	
Eligibility criteria	Adult women (over 18 years of age) with surgically staged advanced epithelial ovarian cancer (FIGO stage III/IV) who had confirmed histological diagnoses. Studies defining optimal cytoreduction as surgery leading to residual tumours with a maximum diameter of any threshold up to 2 cm.
Exclusion criteria	Chemotherapy prior to surgery or other concurrent malignancies
Patient & disease characteristics	A total of 4735 patients were included in all studies (3844 stage III and 891 stage IV); median age for patients with advanced EOC varied between 54 to 64 years (range 16 to 91 years); median duration of follow-up varied from 28 months to 47.5 months (range 1 to 199 months).
Interventions	
Intervention	a) RD >1 cm; b) RD 0.1-1 cm (after primary cytoreductive surgery)
Comparator	No gross RD
Results	
Overall survival	HR (RD < 1 cm vs microscopic disease)= 2.20 (95% CI 1.90 to 2.54) (6 studies) HR (RD >1 cm vs microscopic disease)= 3.16 (95% CI 2.26 to 4.41) (4 studies)
Disease-free survival	Not addressed
Progression-free survival	HR (RD < 1 cm vs microscopic disease)= 1.96 (95% CI 1.72 to 2.23) (2 studies) HR (RD > 1 cm vs microscopic disease) (stage III)= 2.36 (95% CI 2.06 to 2.71) (1 study)
Recurrence rate	Not addressed



Optimal primary surgical treatment for advanced epithelial ovarian cancer; Elattar 2011²⁵⁹

Quality of life	"Quality of life outcomes were not reported by treatment arm or to a satisfactory level in any of the studies."
(loco)regional control	Not addressed
Adverse events	"Adverse events were not reported by treatment arm or to a satisfactory level in any of the studies."
Limitations and comments	
Limitations	Source of funding or support was not reported for each of the included studies. Quality of life outcomes and adverse events were not reported by treatment arm or to a satisfactory level in any of the included studies.

Table 77 – Evidence table (1): observational study prognostic value end result of surgery

Analysis of racial disparities in stage IIIC epithelial ovarian cancer care and outcomes in a tertiary gynecologic oncology referral center; Bristow 2011²⁶⁰

Methods	
Design	Retrospective chart review
Source of funding and competing interest	Source of funding: the Queen of Hearts Foundation for Ovarian Cancer Research Declaration of interest: none declared
Setting	Johns Hopkins Hospital, USA
Sample size	N=433
Duration	Patient enrollment between January 1995 and December 2008
Follow-up	Median follow-up: 33.0 months
Statistical analysis	"Relationships between racial classification and clinic-pathologic variables were compared using Chi ² test of independence and Pearson's R for categorical variables and t-test for continuous variables. OS was calculated from the date of diagnosis using Kaplan–Meier curves and compared using the log-rank test and Cox proportional hazards model."
Patient characteristics	
Eligibility criteria	FIGO Stage IIIC epithelial ovarian cancer based on intra-operative findings or radiographic imaging coupled with fine-needle biopsy diagnosis. All epithelial histological subtypes were included.
Exclusion criteria	Borderline ovarian tumours of low malignant potential.
Patient & disease characteristics	Patient characteristics reported as Whites (n=366) vs African-Americans (n=39) Median age: 59 vs 59 years ASA class, I/II/III/IV: 5/124/232/5 vs 0/4/31/4

Analysis of racial disparities in stage IIIC epithelial ovarian cancer care and outcomes in a tertiary gynecologic oncology referral center; Bristow 2011²⁶⁰

Histology, serous/non-serous: 314/52 vs 31/8
Tumour grade, 1/2/3: 39/33/294 vs 2/4/33
Optimal RD (≤ 1 cm)/no gross RD: 267/188 vs 27/21

Interventions

Intervention group (1)	Optimal debulking (RD 0.1-1.0 cm)
Control group (2)	Complete debulking (no gross RD)

Results

Overall survival	RD 0.1-1.0 cm vs no gross RD: HR= 2.74 (95% CI 1.98 to 3.71) (HR adjusted for age, race, tumour grade, histology, ASA score, surgical complexity score, serum albumin, administration of platinum-based chemotherapy, and significant peri-operative morbidity)
Disease-free survival	Not assessed
Progression-free survival	Not assessed
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Not assessed according debulking status (N/A)

Limitations and other comments

Limitations	Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: study only included women with stage IIIC ovarian cancer / possible overlap with Peiretti 2012.
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**Table 78 – Evidence table (2): observational study prognostic value end result of surgery**

Impact of Complete Cytoreduction Leaving No Gross Residual Disease Associated with Radical Cytoreductive Surgical Procedures on Survival in Advanced Ovarian Cancer; Chang 2012a²⁶¹

Methods

Design	Retrospective review of medical records. The decision to perform a simple or radical procedure for debulking was determined by the surgeon's discretion.
Source of funding and competing interest	Source of funding: one author was supported by the Queen of Hearts Foundation. Declaration of interest: not reported
Setting	Ajou University Hospital, Republic of Korea
Sample size	N=203 of whom 84 underwent a radical surgical procedure and 119 a simple procedure
Duration	Patient enrollment between January 1, 2000 and December 31, 2011
Follow-up	Median 43 months (range 1-124)
Statistical analysis	Chi ² test, Student <i>t</i> and Mann–Whitney <i>U</i> tests. Kaplan–Meier for PFS and OS (including log-rank tests). Univariate and multivariate analyses by the use of Cox proportional hazard model for assessing the influence of various prognostic factors on survival.

Patient characteristics

Eligibility criteria	Consecutive patients with stage IIIC and IV primary epithelial ovarian, fallopian tube, or peritoneal cancer who underwent primary cytoreductive surgery.
Exclusion criteria	Patients who had neoadjuvant chemotherapy, primary cytoreduction at an outside institution, stage IIIC disease based on lymph node metastasis only, or tumours of low malignant potential were excluded.
Patient & disease characteristics	Residual disease: >1 cm/0≤1 cm/no 63/67/63 Median age 54 years (range 30-78). BMI 23.3 (11.7–35.2). FIGO Stage IIIC/IV: 189/14. ASA score 1-2/3-4 114/80 (9 not available). Tumour grade 1/2/3 26/72/100 (5 unknown). Ascites >100 mL: 92. Peritoneal carcinomatosis 149.

Interventions

Intervention group (1)	RD a) macroscopic disease >1 cm ('incomplete') or b) macroscopic disease ≤1 cm ('optimal')
Control group (2)	Complete debulking (no macroscopic disease left in situ)

Results

Overall survival	Median unadjusted OS RD >1 cm 37 months; RD 0.1–1 cm 46 months; no gross RD 86 months. HR (RD >1 cm vs no gross RD)= 3.24 (95% CI 1.90 to 5.53) HR (RD 0.1–1 cm vs no gross RD)= 2.22 (95% CI 1.25 to 3.94)
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Impact of Complete Cytoreduction Leaving No Gross Residual Disease Associated with Radical Cytoreductive Surgical Procedures on Survival in Advanced Ovarian Cancer; Chang 2012a²⁶¹

	HRs adjusted for age, FIGO stage and type of surgery (radical vs simple)
Disease-free survival	Not assessed
Progression-free survival	Median unadjusted PFS RD >1 cm 9 months; RD 0.1–1 cm 15 months; no gross RD 35 months. HR (RD >1cm vs no gross RD)= 2.61 (95% CI 1.58 to 4.29) HR (RD 0.1–1cm vs no gross RD)= 1.97 (95% CI 1.23 to 3.15) HRs adjusted for FIGO stage, tumour grade and type of surgery (radical vs simple)
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Not assessed according debulking status (N/A)
Limitations and other comments	
Limitations	Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: possible overlap with Chang 2012b.

Table 79 – Evidence table (3): observational study prognostic value end result of surgery

Prognostic significance of systematic lymphadenectomy as part of primary debulking surgery in patients with advanced ovarian cancer; Chang 2012b²⁶²

Methods	
Design	Retrospective review of medical records
Source of funding and competing interest	Source of funding: one author was supported by the Queen of Hearts Foundation Declaration of interest: none declared
Setting	Ajou University Hospital, Republic of Korea
Sample size	N=189
Duration	Patient enrollment between January 1, 2000 and December 31, 2011
Follow-up	Not reported (from Figures: max 8 years)

**Prognostic significance of systematic lymphadenectomy as part of primary debulking surgery in patients with advanced ovarian cancer; Chang 2012b²⁶²**

Statistical analysis	Pearson's Chi ² test, Student's t test and Mann–Whitney's U statistic. Kaplan–method for PFS and OS (including log-rank test). Univariate and multivariate analyses by the use of Cox proportional hazard model for assessing the influence of various prognostic factors on survival.
Patient characteristics	
Eligibility criteria	Consecutive patients with stage IIIC primary epithelial ovarian, fallopian tube, or peritoneal cancer who underwent primary cytoreductive surgery and were surgically staged according to the FIGO system. After primary surgery, all patients received adjuvant chemotherapy consisting of cisplatin (75 mg/m ²) or carboplatin (area under the curve; 5–7) and paclitaxel (135 mg/m ²) based systemic combination chemotherapy (every 3 weeks for 6–9 cycles)
Exclusion criteria	Primary cytoreduction at an outside institution, neoadjuvant chemotherapy, stage IIIC disease based on lymph node metastasis only or borderline malignancy
Patient & disease characteristics	Median age 54 years (range 30-78) ASA score, 1-2/3-4/N/A: 107/74/8 Histology, serous/mucinous/endometrioid/clear cell/mixed: 155/4/4/9/17 Tumour grade, 1/2/3: 26/67/91 RD no/0.1–1 cm/>1 cm: 61/67/61 Ascites ≤1000 mL/>1000 mL: 109/80
Interventions	
Intervention group (1)	RD a) >1 cm or b) 0.1-1 cm
Control group (2)	Complete debulking (no gross RD)
Results	
Overall survival	RD 0.1-1 cm vs no gross RD: HR= 2.25 (95% CI 1.25 to 4.03) RD >1 cm vs no gross RD: HR= 3.09 (95% CI, 1.80 to 5.30) HRs adjusted for age, performance of radical surgery and performance of lymphadenectomy
Disease-free survival	Not assessed
Progression-free survival	RD 0.1-1 cm vs no gross RD: HR= 2.03 (95% CI 1.25 to 3.31) RD > 1 cm vs no gross RD: HR= 2.56 (95% CI 1.54 to 4.26) HRs adjusted for performance of radical surgery and performance of lymphadenectomy
Recurrence rate	Not assessed



Prognostic significance of systematic lymphadenectomy as part of primary debulking surgery in patients with advanced ovarian cancer; Chang 2012b²⁶²

Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Not assessed according debulking status (N/A)
Limitations and other comments	
Limitations	Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: study only included women with stage IIIC ovarian cancer / possible overlap with Chang 2012a.

Table 80 – Evidence table (4): observational study prognostic value end result of surgery

The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - analysis of patient data in the prospective OVCAD study; Hofstetter 2013²⁶³

Methods	
Design	Prospective multicenter study
Source of funding and competing interest	Source of funding: the European Union Declaration of interest: none declared
Setting	Multicenter study
Sample size	N=191
Duration	Patient enrollment between August 2005 and December 2008
Follow-up	Median follow-up: 42 months (range 4 to 69 months)
Statistical analysis	Kaplan-Meier curves. Cox proportional hazards model for multivariate analysis. Factors that yielded significant results in the univariate analysis were considered in the multivariate analysis.
Patient characteristics	
Eligibility criteria	Patients with stage IIIA-IV primary ovarian cancer
Exclusion criteria	Neoadjuvant chemotherapy
Patient & disease characteristics	Age ≤57y/>57y: 98/93 ECOG performance status 0/1/2-3: 113/60/10



The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - analysis of patient data in the prospective OVCAD study; Hofstetter 2013²⁶³

FIGO stages IIIA/IIIB/IIIC,no lymph node metastasis/IIIC,lymph node metastasis/IIIC,unknown lymph node status/IV:
4/8/28/92/26/33

Tumour grading I-II/III: 51/140

Postoperative RD microscopic/macrosopic: 121/70

Interventions

Intervention group (1) Macroscopic RD (residual tumour lesions of any size) = "suboptimal RD"

Control group (2) Microscopic RD (no visible residual tumour)

Results

Overall survival Three year OS: HR of microscopic vs macroscopic RD: 2.95 (95% CI 1.87 to 4.67)
HR adjusted for interval between surgery and start of chemotherapy, tumour stage, age and extent of surgery

Disease-free survival Not assessed

Progression-free survival Not assessed

Recurrence rate Not assessed

Quality of life Not assessed

(Loco)regional control Not assessed

Adverse events Not assessed according debulking status (N/A)

Limitations and other comments

Limitations

Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: possible overlap with Polterauer 2012

**Table 81 – Evidence table (5): observational study prognostic value end result of surgery**

Morbidity, mortality and overall survival in elderly women undergoing primary surgical debulking for ovarian cancer: A delicate balance requiring individualization; Langstraat 2011²⁶⁴

Methods	
Design	Retrospective review of medical records
Source of funding and competing interest	Source of funding: not reported Declaration of interest: none
Setting	Mayo Clinic, USA
Sample size	N=280
Duration	Patient enrollment between January 1, 1994 and December 31, 2004
Follow-up	Mean follow-up: 3.2 years (range 0–15.8 years)
Statistical analysis	Chi-square or student T-tests, Kaplan–Meier curves. Statistically significant predictors of OS (p<0.05) identified in univariate analysis were further analysed in a multivariate Cox-proportional hazard model.
Patient characteristics	
Eligibility criteria	Patients with stage IIIC–IV primary ovarian cancer and managed with the intention of complete tumour cytoreduction (residual disease (RD)=0) followed by treatment with Taxol and platinum-based chemotherapy. Patients had to be 65 years of age and older.
Exclusion criteria	Patients which received neoadjuvant chemotherapy, underwent initial surgical debulking at another facility or had borderline tumour histology or non-epithelial cancer. Patients who required emergent/urgent surgical intervention due to a small bowel obstruction were included if the stated primary surgical goal was to achieve complete cytoreduction, otherwise they were excluded.
Patient & disease characteristics	Mean age 73.5 years (range 65–89) ASA 1-2/3-4: 96/181 Stage IIIC/IV: 210/67 Histologic types: serous 205, mucinous 6, endometrioid 17, clear cell 6, other 43 (missing: 3)
Interventions	
Intervention group (1)	a) RD >1 cm; b) RD 0.1-1 cm
Control group (2)	No gross RD
Results	
Overall survival	HR (RD >1 cm vs no gross RD)= 4.51 (95%-CI 2.92 to 7.17)



Morbidity, mortality and overall survival in elderly women undergoing primary surgical debulking for ovarian cancer: A delicate balance requiring individualization; Langstraat 2011²⁶⁴

	HR (RD 0-1 cm vs no gross RD)= 2.24 (95%-CI 1.48 to 3.49) HRs adjusted for creatinine, surgical complexity score, FIGO stage, and age group.
Disease-free survival	Not assessed
Progression-free survival	Not assessed
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Not assessed
Limitations and other comments	
Limitations	Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: study only included women aged 65 years of older.

Table 82 – Evidence table (6): observational study prognostic value end result of surgery

Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: Surgical and oncological outcomes. Single institution experience; Peiretti 2010²⁶⁵

Methods	
Design	Retrospective review of medical records
Source of funding and competing interest	Source of funding: not reported Declaration of interest: none
Setting	Single centre, Italy
Sample size	N=259 consecutive patients
Duration	Patient enrollment between January 2001 and December 2008
Follow-up	Median follow-up 29.8 months



Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: Surgical and oncological outcomes. Single institution experience; Peiretti 2010²⁶⁵

Statistical analysis	Kaplan–Meier to estimate survival curves; differences in survival were analyzed by the log-rank test. Cox proportional hazards regression to identify independent prognostic variables for OS by univariate and multivariate analyses
Patient characteristics	
Eligibility criteria	Patients with stages IIIC–IV epithelial ovarian and fallopian tube cancer who underwent maximal primary cytoreductive surgery
Exclusion criteria	Prior attempt of surgical cytoreduction at another institution, histology consistent with non-epithelial ovarian malignancies or borderline tumours and neoadjuvant chemotherapy treatment
Patient & disease characteristics	<p>Median age 58 years (range 22–77)</p> <p>Primary site: ovary/fallopian tube: 256/3</p> <p>FIGO stage: IIIC/IV 199/60</p> <p>Tumour grade 1-2/3/N/A: 53/198/8</p> <p>Histologic type: serous 184, endometrioid 39, clear cell 8, mixed 26, other 2</p> <p>Peritoneal carcinomatosis 188</p>
Interventions	
Intervention group (1)	Any RD
Control group (2)	No grossly visible RD
Results	
Overall survival	<p>Unadjusted median OS: not reached for no gross RD; 61.3 months for 1–5 mm; 42.4 months for 6–10 mm; 35.3 months for 10–20 mm; 42.6 months for ≥20 mm</p> <p>No multivariate analysis performed for OS according to debulking status</p>
Progression-free survival	Multivariate analysis: “Age greater than 60 years ($p=0.025$), stage IV vs IIIC ($p=0.037$) and any residual disease ($p=0.032$) had an independent association with worse PFS.”
Disease-free survival	Not assessed
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Not assessed



Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: Surgical and oncological outcomes. Single institution experience; Peiretti 2010²⁶⁵

Limitations and other comments

Limitations Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: possible overlap with Peiretti 2012.

Table 83 – Evidence table (7): observational study prognostic value end result of surgery

Rectosigmoid resection at the time of primary cytoreduction for advanced ovarian cancer. A multi-center analysis of surgical and oncological outcomes; Peiretti 2012²⁶⁶

Methods

Design	Retrospective review of medical records
Source of funding and competing interest	Source of funding: not reported Declaration of interest: none declared
Setting	Gynecologic Oncology at the European Institute of Oncology, Milan, Italy (157 patients) Kelly Gynecologic Oncology Service, Johns Hopkins Medical Institutions, Baltimore, USA (81 patients)
Sample size	N=238 consecutive patients
Duration	Patient enrollment between August 1998 and July 2008
Follow-up	Not reported
Statistical analysis	Kaplan–Meier to estimate survival curves; differences in survival were analyzed by the log-rank test. Cox proportional hazards regression to identify independent prognostic variables for OS by univariate and multivariate analyses

Patient characteristics

Eligibility criteria	Patients with advanced epithelial ovarian cancer who underwent rectosigmoid colectomy at the time of primary cytoreductive surgery
Exclusion criteria	Neoadjuvant treatment
Patient & disease characteristics	Median age 59.7 years (range 22–85) Primary site: ovary/fallopian tube/peritoneum: 230/4/4 FIGO stage: IIC/IIIA/IIIB/IIIC/IV 3/1/2/174/58



Rectosigmoid resection at the time of primary cytoreduction for advanced ovarian cancer. A multi-center analysis of surgical and oncological outcomes; Peiretti 2012²⁶⁶

Tumour grade 1-2/3/N/A: 51/184/3

Histologic type: serous 200, endometrioid 15, clear cell 5, mixed 18

Interventions

Intervention group (1) Any other gross RD

Control group (2) No grossly visible RD

Results

Overall survival Unadjusted median OS: any gross RD vs no macroscopic RD: 42 months vs 72 months ($p=0.002$)
"Presence of any macroscopic residual disease at the end of surgery was the only identified risk factor for OS ($p=0.003$)"

Progression-free survival Not assessed

Disease-free survival Not assessed

Recurrence rate Not assessed

Quality of life Not assessed

(Loco)regional control Not assessed

Adverse events Not assessed

Limitations and other comments

Limitations Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: only women who underwent rectosigmoid colectomy were included / possible overlap with Bristow 2011 and Peiretti 2010.

**Table 84 – Evidence table (8): observational study prognostic value end result of surgery**

Prognostic Value of Residual Tumour Size in Patients With Epithelial Ovarian Cancer FIGO Stages IIAYIV; Polterauer 2012 ²⁶⁷	
Methods	
Design	Prospective multicenter study
Source of funding and competing interest	Source of funding: the European commission (FP6 Specific Targeted Research or Innovation Project) Declaration of interest: none declared
Setting	Multicenter study (5 specialized European centers for gynecologic oncology)
Sample size	N=226
Duration	Patient enrollment between February 2005 and December 2008
Follow-up	Median follow-up: 25.0 months (range 1-49)
Statistical analysis	Chi ² tests. Univariate survival analysis of categorical variables by the log-rank test. Multiple forward stepwise Cox regression analysis.
Patient characteristics	
Eligibility criteria	Patients with epithelial ovarian cancer FIGO Stages IIA-IV in whom radical cytoreductive surgery was performed and standard chemotherapy with paclitaxel and carboplatin was applied.
Exclusion criteria	Patients having received neoadjuvant chemotherapy followed by interval debulking.
Patient & disease characteristics	Mean age 57.5 year (SD 11.9) FIGO stages II, III and IV: 15 (6.6%), 174 (76.9%), and 37 (16.4%); FIGO stages IIIC and IV: 198 patients (87.6%) Histological type serous/other: 194/32 No macroscopic residual disease: 69.4% Minimal residual disease (≤ 1 cm): 87.2% (NB: this category also includes the No RD category!)
Interventions	
Intervention group (1)	Any RD (cq minimal RD (≤ 1 cm) or gross RD (> 1 cm))
Control group (2)	Complete debulking (no RD)
Results	
Overall survival	3-year OS (unadjusted) with no RD: 72.4%; minimal RD: 65.8%; gross RD: 45.2% Subgroup analysis of stages IIIC and IV: 3-year OS (unadjusted) with no RD 69.7% (SE= 5.3%); any RD 53.6% (SE= 8.3%) (P = 0.003)



Prognostic Value of Residual Tumour Size in Patients With Epithelial Ovarian Cancer FIGO Stages IIAYIV; Polterauer 2012²⁶⁷

	HR (apparently for 'Any RD' vs 'No RD', adjusted for FIGO-stage, histological grade, histological type and age) = 1.4 (95%-CI 1.0 to 2.1) "Multivariable survival analysis revealed residual tumour size (p=0.04) and older patient age (p =0.02) as independent prognosticators for impaired overall survival. Complete cytoreduction was predictive for a higher rate of treatment response (p=0.001) and was associated with prolonged progression-free and overall survival (p<0.001 and p=0.001)."
Disease-free survival	Not assessed
Progression-free survival	HR (apparently for 'Any RD' vs 'No RD', adjusted for FIGO-stage, histological grade, histological type and age) = 1.6 (95%-CI 1.3 to 2.1)
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Not assessed
Limitations and other comments	
Limitations	Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Patient and disease characteristics not reported according to debulking status. NB: possible overlap with Hofstetter 2013

**Table 85 – Evidence table (9): observational study prognostic value end result of surgery**

Upper abdominal procedures in advanced stage ovarian or primary peritoneal carcinoma patients with minimal or no gross residual disease: an analysis of Gynecologic Oncology Group (GOG) 182; Rodriguez 2013²⁶⁸

Methods	
Design	Retrospective analysis of data from Gynecologic Oncology Group-182 (GOG-182), a prospective, multi-institutional clinical trial.
Source of funding and competing interest	Source of funding: National Cancer Institute Declaration of interest: "Dr. Michael Bookman has no financial relationships relevant to this manuscript. However, he currently serves as Chair, Ovarian Committee, GOG, and also serves as Principal Investigator for GOG0182-ICON5. All other co-authors have no conflicts of interest to declare."
Setting	Multicenter study
Sample size	N=2655
Duration	Patient enrollment between February 2001 and September 2004
Follow-up	Not reported (from Figures: max. 108 months)
Statistical analysis	"Multivariate modeling methods were used to adjust the treatment effect estimate for baseline imbalances. The effects of upper abdominal procedures (UAPs) vs NUAPs on OS and PFS were modeled using multivariable proportional hazards methods. The OS and PFS results were further illustrated with Kaplan Meier methods, with distributional difference assessed using the logrank test."
Patient characteristics	
Eligibility criteria	Patients who had FIGO stage III or IV disease and were optimally cytoreduced (maximal residual tumour diameter <1 cm) following primary cytoreductive surgery.
Exclusion criteria	No optimal cytoreduction
Patient & disease characteristics	Mean age, years (NUAP vs UAP): 58.5 vs 57.1 Histology, Serous/endometrioid/mucinous/clear cell/mixed/transitional/undiffer: 2152/141/35/102/156/15/34 Grade 1/2/3: 111/478/1590 Stage 3/4: 2364/291 Residual disease: complete/minimal (<1 cm): 860/1795
Interventions	
Intervention group (1)	RD 0.1-1.0 cm
Control group (2)	Complete resection (no visible RD)



Upper abdominal procedures in advanced stage ovarian or primary peritoneal carcinoma patients with minimal or no gross residual disease: an analysis of Gynecologic Oncology Group (GOG) 182; Rodriguez 2013²⁶⁸

Results

Overall survival “Patients with complete reduction of disease had better prognosis than those with <1 cm ($p < 0.01$). This advantage showed a trend towards an improved OS in the matched sample of patients with complete reduction with a UAP (HR=0.61, 95% CI: 0.36 to 1.01, $p = 0.06$), and this was not seen in the full sample of patients (HR=0.80, 95% CI: 0.56 to 1.16, $p = 0.24$).”

In patients who underwent an UAP ($n = 141$): OS of complete reduction (no RD) vs RD <1: 54.6 vs 40.4 months

Disease-free survival Not assessed

Progression-free survival In patients who underwent an UAP ($n = 141$): PFS of complete reduction (no RD) vs RD <1: 20.2 vs 13.7 months
“Patients with completely resected disease had better PFS than those with <1 cm ($p < 0.01$).”

Recurrence rate Not assessed

Quality of life Not assessed

(Loco)regional control Not assessed

Adverse events Not assessed according debulking status (N/A)

Limitations and other comments

Limitations Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs derived from a sound multivariate analysis.
Patient and disease characteristics not reported according to debulking status. NB: women with RD >1 cm were excluded.

Table 86 – Evidence table (10): observational study prognostic value end result of surgery

Influence of Residual Tumour on Outcome in Ovarian Cancer patients With FIGO Stage IV Disease; Wimberger 2010²⁶⁹

Methods

Design Retrospective data set review (retrieved from three prospective, randomized phase III trials: AGO-OVAR (OVAR-3/-5/-7))

Source of funding and competing interest Source of funding: grants for the phase III study AGO-OVAR 3 from Bristol-Myers-Squibb, for the AGO-OVAR 5 from Pfizer, and for AGO-OVAR 7 from Glaxo Smith Kline.
Declaration of interest: not reported



Influence of Residual Tumour on Outcome in Ovarian Cancer patients With FIGO Stage IV Disease; Wimberger 2010²⁶⁹

Setting	Multicenter, Germany and France (AGO-OVAR and GINECO)
Sample size	N=573
Duration	Enrollment between 1995 and 2002
Follow-up	Not described
Statistical analysis	Kaplan–Meier; log rank test. Multivariable Cox regression models to analyze the impact of residual tumour on survival, adjusting for other predictors of survival.
Patient characteristics	
Eligibility criteria (retrieved from previous publications)	<p>Previously untreated epithelial ovarian cancer FIGO stage IV, at least 18 years of age and required to have adequate hematologic, renal, and hepatic function, defined as follows: absolute neutrophil count (ANC) of at least 1.5×10^9 cells/L, platelet count of at least 100×10^9 cells/L, serum creatinine and bilirubin of no more than $1.25 \times$ upper normal limit.</p> <p>All patients received platinum- and paclitaxel-based chemotherapy within 6 weeks after cytoreduction surgery (object of study in the various underlying RCTs)</p>
Exclusion criteria (retrieved from previous publications)	<p>Ovarian tumours with low malignant potential; an Eastern Cooperative Oncology Group performance status of more than 2 or a Karnofsky index of less than 60%; an estimated glomerular filtration rate (GFR) of less than 60 mL/minute; other malignancies; previous chemo-, immuno-, or radiotherapy for ovarian cancer; severe neuropathy; cardiac arrhythmias; or congestive heart failure.</p> <p>“In addition, we excluded patients from this exploratory analysis if metric data about intra- and postoperative findings or details about surgical procedures were not completely documented.”</p>
Patient & disease characteristics	<p>Patient characteristics for the subgroup with FIGO stage IV disease:</p> <p>Median age: 59.0 years (range, 19–83 years)</p> <p>Histologic type: serous cell 68.2%, mucinous subtype 6.9%</p> <p>Microscopic RD 12.3%, RD 0.1 to 1 cm 29.3%, RD 1 cm 58.4%</p> <p>Peritoneal carcinomatosis 87.8%</p>
Interventions	
Intervention group (1)	a) RD 0.1–1 cm and b) RD >1 cm
Control group (2)	Complete resection (no visible RD)

Influence of Residual Tumour on Outcome in Ovarian Cancer patients With FIGO Stage IV Disease; Wimberger 2010²⁶⁹**Results**

Overall survival	<p>Patients with stage IV</p> <p>Median OS (unadjusted) of no RD vs RD 0.1-1.0 cm vs RD >1 cm: 54.6 vs 25.8 vs 23.9 months ($p < 0.0001$)</p> <p>RD 0.1-1 cm vs no visual RD: HR= 1.87 (95% CI 1.21 to 2.89)</p> <p>RD >1 cm vs no visual RD: HR= 2.13 (95% CI 1.40 to 3.23)</p> <p>HRs adjusted for age, performance status, histological type, presence of peritoneal carcinomatosis and multiple sites (Y/N)</p>
Disease-free survival	Not assessed
Progression-free survival	<p>Patients with stage IV</p> <p>Median PFS (unadjusted) of no RD vs RD 0.1-1.0 cm vs RD >1 cm: 19.1 vs 13.6 vs 11.3 months ($p < 0.0001$)</p> <p>RD 0.1-1 cm vs no visual RD: HR= 1.51 (95% CI 1.05 to 2.19)</p> <p>RD >1 cm vs no visual RD: HR= 1.82 (95% CI 1.28 to 2.59) (NB: error in Table 2: lower limit = 1.28 instead of 0.28)</p> <p>HRs adjusted for age, performance status, histological type, presence of peritoneal carcinomatosis and multiple sites (Y/N)</p>
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Not assessed
Limitations and other comments	
Limitations	<p>Retrospective non-randomised study. Blinding not reported (but not applicable). Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance).</p> <p>Patient and disease characteristics not reported according to debulking status. NB: only women with stage IV were included.</p>



5.7.2. Effect of (ultra)radical surgery

Table 87 – Evidence table: SR effect of (ultra)radical surgery

Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer; Ang 2011333	
Methods	
Design	Cochrane systematic review
Source of funding and competing interest	Department of Health, UKNHS Cochrane Collaboration programme Grant Scheme CPG-506 Declaration of interest: none
Search date	November 2010
Searched databases	MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Gynaecological Cancer Group Trials Register. Furthermore, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contact with experts in the field.
Included study designs	RCTs, quasi-randomised trials; non-randomised trials, prospective and retrospective cohort studies, and case series of 100 or more patients, that used statistical adjustment for baseline case mix using multivariate analyses. Case-control studies, uncontrolled observational studies and case series of fewer than 100 patients were excluded.
Number of included studies	One retrospective analysis of 194 patients from the Mayo clinic in Rochester
Statistical analysis	No meta-analysis was performed
Patient characteristics	
Eligibility criteria	Adult women with stage III or IV epithelial ovarian cancer, who had ultra-radical surgery as part of interval debulking surgery
Exclusion criteria	Women with other concurrent malignancies or women with recurrent disease
Patient & disease characteristics*	Included: 194 women with stage IIIC ovarian cancer (numbers per type of intervention not reported) Mean age 64.4 years (range 24 to 87) Histologic types: serous 65%; endometrioid, mixed and seroanaplastic 27%, other 18% Grade III tumour 93% ASA score 2 or 3 90% Mean and median volume of ascites: 2076 ml and 1,000 ml (range: 0 to 12,000 ml)
Interventions*	
Intervention group	Ultra-radical surgery: surgery in which any diaphragmatic surgery, bowel resection, splenectomy, or extensive abdominal peritoneal stripping or resection was performed



Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer; Ang 2011333

Control group	Standard surgery: if none of the above-mentioned procedures were performed, but hysterectomy, complete omentectomy, stripping of pelvic peritoneum, or limited resection of peritoneal-based nodules was carried out
Results*	
Overall survival	Not assessed
Disease-free survival	Not assessed Disease-specific survival: HR for death from advanced epithelial ovarian cancer (adjusted for age, ASA score, carcinomatosis, mesenteric involvement, diaphragmatic involvement, ascites, residual disease and operative time): 0.64 (95% CI 0.40 to 1.04) "Women who had ultra-radical surgery had better disease specific survival than those who underwent standard surgery (NS)"
Progression-free survival	Not assessed
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Perioperative mortality (death within 2 weeks following surgery): 0 vs 3 women (not adjusted for baseline imbalances)
Limitations and other comments	
Limitations	No RCTs were identified. Only one comparative observational study could be included. Many of the objectives of the review could not be met. Main outcomes of interest were not addressed

Table 88 – Evidence table (1): Observational study effect of (ultra)radical surgery

Impact of Complete Cytoreduction Leaving No Gross Residual Disease Associated with Radical Cytoreductive Surgical Procedures on Survival in Advanced Ovarian Cancer; Chang 2012²⁶¹

Methods	
Design	Retrospective review of medical records. The decision to perform simple or radical procedures was determined by the surgeon's discretion.
Source of funding and competing interest	Source of funding: One author was supported by the Queen of Hearts Foundation. Declaration of interest: not reported
Setting	Ajou University Hospital, Republic of Korea



Impact of Complete Cytoreduction Leaving No Gross Residual Disease Associated with Radical Cytoreductive Surgical Procedures on Survival in Advanced Ovarian Cancer; Chang 2012²⁶¹

Sample size	N=203 of whom 84 underwent a radical surgical procedure and 119 a simple procedure
Duration	Patient enrollment between January 1, 2000 and December 31, 2011
Follow-up	Median 43 months (range 1-124)
Statistical analysis	Clinical and pathologic factors were compared with Pearson's Chi2 test. The Student t and Mann–Whitney U tests were used for continuous data according to normality. Kaplan–Meier for PFS and OS (including log-rank tests). Univariate and multivariate analyses for assessing the influence of various prognostic factors on survival was performed by the Cox proportional hazard model.
Patient characteristics	
Eligibility criteria	Consecutive patients with stage IIIC and IV primary epithelial ovarian, fallopian tube, or peritoneal cancer who underwent primary cytoreductive surgery.
Exclusion criteria	Patients who had neoadjuvant chemotherapy, primary cytoreduction at an outside institution, stage IIIC disease based on lymph node metastasis only, or tumours of low malignant potential were excluded.
Patient & disease characteristics	Median age 54 years (range 30-78). BMI 23.3 (11.7–35.2). FIGO Stage IIIC/IV: 189/14. ASA score 1-2/3-4 114/80 (9 not available). Tumour grade 1/2/3 26/72/100 (5 unknown). Ascites >100 mL: 92. Peritoneal carcinomatosis 149. Residual disease: no/≤1/1cm 63/67/63
Interventions	
Intervention group (1)	Radical cytoreductive procedures included radical oophorectomy with or without rectosigmoid colectomy, total omentectomy, multiple bowel resections, diaphragm peritonectomy or resection, liver resection, splenectomy, distal pancreatectomy, and gastric resection. After surgery, all patients received adjuvant platinum-based chemotherapy in combination with paclitaxel for 6–9 cycles.
Control group (2)	Simple surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal biopsies or excisions, infracolic omentectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy, and segmental resection of small bowel. After surgery, all patients received adjuvant platinum-based chemotherapy in combination with paclitaxel for 6–9 cycles.
Results	
Overall survival	Median 66 vs 38 months (p= 0.01; unadjusted) HR (adjusted for age, FIGO stage and residual disease): 0.56 (95% CI 0.37 to 0.87)
Disease-free survival	Not assessed

**Impact of Complete Cytoreduction Leaving No Gross Residual Disease Associated with Radical Cytoreductive Surgical Procedures on Survival in Advanced Ovarian Cancer; Chang 2012²⁶¹**

Progression-free survival	Median 18 vs 11 months (p= 0.01; unadjusted) HR (adjusted for FIGO stage, tumour grade and residual disease): 0.62 (95% CI 0.42 to 0.92)
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed
Adverse events	Significant postoperative morbidity 32/84 (38.1%) vs 14/119 (11.8%); RR= 3.24 (95% CI 1.84 to 5.68) Postoperative death within 30 days 1/84 (1.2%) vs 0/119 (0%); RR= 4.24 (95% CI 0.17 to 102.72) “Patients who underwent radical surgery had significantly longer operative time, larger estimated blood loss, more blood transfusions, longer stay in the intensive care unit, and more lymphocysts than those who underwent simple surgery.”
Limitations and other comments	
Limitations	Retrospective non-randomised study. The decision to perform simple or radical procedures was determined by the surgeon's discretion. Confounding by indication can't be excluded. Patient and disease characteristics not reported per type of surgery. Blinding not reported. Adjusted HRs are derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance).

Table 89 – Evidence table (2): Observational study effect of (ultra)radical surgery**Maximal Cytoreduction in Patients With FIGO Stage IIIC to Stage IV Ovarian, Fallopian, and Peritoneal Cancer in Day-to-Day Practice; Luyckx 2012³⁰²**

Methods	
Design	Retrospective review of medical records of patients treated in 7 French gynaecologic oncology and surgery centers.
Source of funding and competing interest	No funding source reported. The authors declared no conflicts of interest.
Setting	Seven leading French gynaecologic oncology units
Sample size	N=527 of whom 124 underwent a radical surgical procedure and 290 a simple procedure (113 patients ignored for KCE's RQ)



Maximal Cytoreduction in Patients With FIGO Stage IIIC to Stage IV Ovarian, Fallopian, and Peritoneal Cancer in Day-to-Day Practice; Luyckx 2012³⁰²

Duration	Patient enrollment between January 1, 2003 and December 31, 2007
Follow-up	Median 49 months
Statistical analysis	Univariate and multivariate analyses for assessing the influence of various prognostic factors on survival was performed by the Cox proportional hazard model.
Patient characteristics	
Eligibility criteria	Patients with stage IIIC and stage IV (pleural invasion only) ovarian, tubal, or peritoneal epithelial carcinoma who underwent either primary or interval debulking. All had at least 6 cycles of carboplatin and paclitaxel combination. No bevacizumab was used in any patient.
Exclusion criteria	FIGO stage IIIC as defined by lymph nodes invasion only, patients in whom surgical procedures were not detailed enough in the operative reports to allow a retrospective scoring, and patients with nonepithelial histological subtypes or borderline cancer were excluded.
Patient & disease characteristics	Median age 59 years (range 24-90). FIGO Stage IIIC/IV: 441/86. Tumour grade 1/2/3 34/138/236 (119 unknown). Primary/Interval debulking 190/268. Ascites: median 50 mL (range 0-8000). Peritoneal cancer index: median 10. Residual disease: 0/≤1/>1cm 374/97/55. Upper abdominal lesion 0/≤2.5/>2.5 cm 175/182/97 (73 unknown).
Interventions	
Intervention group (1)	Ultra-radical surgery involving a combination of digestive tract resections (right colon and cecum, total colectomy, and others), organ resection (spleen, gallbladder, partial gastrectomy, and others), celiac lymph node dissection, and total abdominal peritoneum stripping in addition to standard surgery (group 2B in the study).
Control group (2)	Standard surgery with hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection, infragastric omentectomy, pelvic and aortic lymphadenectomy, and, when applicable, appendectomy (group 1 in the study)
Results	
Overall survival	No significant differences between surgical groups in the univariate analysis. Multivariate analysis not performed.
Disease-free survival	Median 15.9 vs 19.3 months (significant; not adjusted). HR for relapse or death (adjusted for FIGO stage, tumour grade, presence of upper abdominal disease, amount of residual disease and timing of surgery (primary or interval): 1.66 (95% CI 1.16 to 2.39)
Progression-free survival	Not assessed
Recurrence rate	Not assessed
Quality of life	Not assessed
(Loco)regional control	Not assessed



Maximal Cytoreduction in Patients With FIGO Stage IIIC to Stage IV Ovarian, Fallopian, and Peritoneal Cancer in Day-to-Day Practice; Luyckx 2012³⁰²

Adverse events Not assessed

Limitations and other comments

Limitations

Retrospective non-randomised study. We assume that the decision to perform simple or radical procedures was determined by the surgeon's discretion. Confounding by indication can't be excluded.

Patient and disease characteristics not reported per type of surgery. Blinding not reported (but may not be relevant to this research question).

Sample also included a mixture of primary and interval debulking surgery.

Adjusted HRs are derived from a prognostic model. Characteristics were selected based on statistical significance in the univariate analysis ($p < 0.10$) and not on including putative confounders in the analysis, irrespective of statistical significance.

5.8. Neo-adjuvant chemotherapy and interval debulking versus upfront surgery

5.8.1. Systematic reviews

Table 90 – Evidence table: SRs neo-adjuvant chemotherapy and interval debulking versus upfront debulking followed by chemotherapy

Morrison J 2012³⁸²

Methods

Design SR

Source of funding and competing interest Sean Kehoe is lead investigator in the CHORUS # study
Supported by 10/4001/12 NIHR Cochrane Programme Grant Scheme, UK

Search date August 2011

Searched databases Specialised Register of the Cochrane Gynaecological Cancer Group; EMBASE via Ovid; MEDLINE; CENTRAL; PDQ and MetaRegister

Included study designs RCTs

Number of included studies N=1

Statistical analysis Not applicable

Patient characteristics

Eligibility criteria Women with advanced epithelial ovarian cancer (FIGO stage III/IV)

Morrison J 2012³⁸²

Exclusion criteria	Not specifically stated
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Patient & disease characteristics	See Vergote 2010
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Interventions

Intervention group	Primary debulking surgery, with the aim to leave no residual disease > 2 cm, followed by platinum-based chemotherapy
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Control group	Platinum-based neoadjuvant chemotherapy followed by debulking surgery (with the aim to leave no residual disease > 2 cm)
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Results

See Vergote 2010

Limitations and other comments

Comments	Three ongoing studies identified: CHORUS, Kumar et al., Onda et al.
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**Characteristics apply to the only included non-randomised study*

5.8.2. RCTs

Table 91 – Evidence table (1): RCTs neo-adjuvant chemotherapy and interval debulking versus upfront debulking followed by chemotherapy

Vergote I 2010, Greimel E 2013 ^{293, 330}
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Methods

Design	RCT
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Source of funding and competing interest	National Cancer Institute, EORTC
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Setting	Multicentre, worldwide (59 centres)
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Sample size	N=670
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Duration and follow-up	9/1998-12/2006
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Statistical analysis	Overall and progression-free survival rates were estimated by means of the Kaplan-Meier method, and overall survival rates in the two groups were compared by means of the log-rank test, with a noninferiority ratio of 0.8. Multivariate time-to-event analysis was performed with the use of a Cox proportional-hazards model and univariate screening followed by a stepwise variable-selection procedure.
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Vergote I 2010, Greimel E 2013^{293, 330}**Patient characteristics****Eligibility criteria**

Patients with biopsy-proven stage IIIC or IV invasive epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian-tube carcinoma

If a biopsy specimen was not available, a FNA showing an adenocarcinoma was acceptable under the following conditions:

the presence of a pelvic (ovarian) mass;

the presence of metastases outside the pelvis measuring at least 2 cm in diameter (as noted during diagnostic laparoscopy or laparotomy or on CT);

regional lymph-node metastasis or proof of stage IV disease; and

a ratio of CA-125 to CEA > 25

If the ratio of CA-125 to CEA was 25 or lower, results of a barium enema (or colonoscopy), gastroscopy (or radiologic examination of the stomach), and mammography (performed within 6 weeks before randomization) had to be negative for the presence of a primary tumour

Additional criteria:

WHO performance status 0-2

Absence of serious disabling diseases that would contraindicate primary cytoreductive surgery or platinum-based chemotherapy

Patient & disease characteristics

Median age: 62 vs. 63 years

Primary tumour epithelial ovarian: 87.2% vs. 84.7%

Serous histology: 66% vs. 58%

Stage IIIC: 77% vs. 76%; stage IV: 23% vs. 24%

Interventions**Intervention group**

Primary debulking surgery followed by at least 6 courses of platinum-based chemotherapy (interval debulking surgery was permitted when surgery was completed without optimal cytoreduction and if stable disease or a response was documented) (PDS group, N=336)

Control group

Neo-adjuvant platinum-based chemotherapy followed by interval debulking surgery in all patients with a response or stable disease, followed in turn by at least three courses of platinum-based chemotherapy (NACT group, N=334)

Results**Overall survival**

Median: 29 vs. 30 months



Vergote I 2010, Greimel E 2013^{293, 330}

	HR for death in NACT group: 0.98 (90%CI 0.84-1.13, p=0.01 for noninferiority) Among patients with metastatic tumours < 5 cm in diameter at randomization, overall survival was slightly longer in the PDS group than in the NACT group (HR 0.64; 95%CI 0.45-0.93)
Progression-free survival	Median: 12 months in both groups HR for progressive disease: 1.01 (90%CI 0.85-1.16, p=0.01)
Adverse events	Postoperative death (within 28 days after surgery): 2.5% vs. 0.7% Grade 3-4 hemorrhage: 7.4% vs. 4.1% Infection: 8.1% vs. 1.7% Venous complications: 2.6% vs. 0%
Quality of life (Greimel 2013)	Based on EORTC QLQ-C30 data of 404 patients (PDS: N=201; NACT: N=203) Minimal clinically significant difference was defined as 10 points No statistically significant differences between the treatment arms in any of the QOL functioning or symptoms scales except for pain and dyspnoea: Pain: mean (SD) 6m follow-up: PDS 19.0 (3.8) vs. NACT 15.4 (3.6) 12m follow-up: PDS 19.1 (4.2) vs. NACT 15.1 (3.9) Overall post-baseline differences between treatment arms: p=0.046 Dyspnoea: mean (SD) 6m follow-up: PDS 16.8 (3.9) vs. NACT 16.3 (3.7) 12m follow-up: PDS 15.6 (4.3) vs. NACT 18.9 (4.0) Overall post-baseline differences between treatment arms: p=0.049
Limitations and other comments	
Limitations	Central randomization at EORTC Blinding not mentioned (but not realistic for patients and clinicians) ITT-analysis, except for quality of life Non-inferiority study For quality of life, the sample size was reduced. Statistically significant differences were found between the 404 selected patients and the overall population of 670 patients

**Table 92 – Evidence table (2): RCTs neo-adjuvant chemotherapy and interval debulking versus upfront debulking followed by chemotherapy**

Kehoe 2015 ⁴¹⁴	
Methods	
Design	RCT
Source of funding and competing interest	Cancer Research UK and the Royal College of Obstetricians and Gynaecologists; five authors are employed by the Medical Research Council. The other authors declare no competing interests.
Setting	Multicentre, UK and New-Zealand (59 centres)
Sample size	N=550
Duration and follow-up	9/1998-12/2006
Statistical analysis	Non-inferiority study Overall and progression-free survival survival: Kaplan-Meier method, comparison using stratified log-rank test Quality of life: analysis of covariance with adjustment for baseline scores Stata 12 or later
Patient characteristics	
Eligibility criteria	Patients with biopsy-proven stage IIIC or IV invasive epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian-tube carcinoma If a biopsy specimen was not available, a FNA showing an adenocarcinoma was acceptable under the following conditions: the presence of a pelvic (ovarian) mass; the presence of metastases outside the pelvis measuring at least 2 cm in diameter (as noted during diagnostic laparoscopy or laparotomy or on CT); regional lymph-node metastasis or proof of stage IV disease; and a ratio of CA-125 to CEA > 25 If the ration of CA-125 to CEA was 25 or lower, results of a barium enema (or colonoscopy), gastroscopy (or radiologic examination of the stomach), and mammography (performed within 6 weeks before randomization) had to be negative for the presence of a primary tumour Additional criteria: WHO performance status 0-2 Absence of serious disabling diseases that would contraindicate primary cytoreductive surgery or platinum-based chemotherapy

Kehoe 2015⁴¹⁴

Patient & disease characteristics	Median age: 62 vs. 63 years Primary tumour epithelial ovarian: 87.2% vs. 84.7% Serous histology: 66% vs. 58% Stage IIIC: 77% vs. 76%; stage IV: 23% vs. 24%
Interventions	
Intervention group	Primary debulking surgery followed by at least 6 courses of platinum-based chemotherapy (interval debulking surgery was permitted when surgery was completed without optimal cytoreduction and if stable disease or a response was documented) (PDS group, N=336)
Control group	Neoadjuvant platinum-based chemotherapy followed by interval debulking surgery in all patients with a response or stable disease, followed in turn by at least three courses of platinum-based chemotherapy (NACT group, N=334)
Results	
Overall survival	Median: 29 vs. 30 months HR for death in NACT group: 0.98 (90%CI 0.84-1.13, p=0.01 for noninferiority) Among patients with metastatic tumours < 5 cm in diameter at randomization, overall survival was slightly longer in the PDS group than in the NACT group (HR 0.64; 95%CI 0.45-0.93)
Progression-free survival	Median: 12 months in both groups HR for progressive disease: 1.01 (90%CI 0.85-1.16, p=0.01)
Adverse events	Postoperative death (within 28 days after surgery): 2.5% vs. 0.7% Grade 3-4 hemorrhage: 7.4% vs. 4.1% Infection: 8.1% vs. 1.7% Venous complications: 2.6% vs. 0%
Quality of life (Greimel 2013)	Based on EORTC QLQ-C30 data of 404 patients (PDS: N=201; NACT: N=203) Minimal clinically significant difference was defined as 10 points No statistically significant differences between the treatment arms in any of the QOL functioning or symptoms scales except for pain and dyspnoea: Pain: mean (SD) 6m follow-up: PDS 19.0 (3.8) vs. NACT 15.4 (3.6) 12m follow-up: PDS 19.1 (4.2) vs. NACT 15.1 (3.9) Overall post-baseline differences between treatment arms: p=0.046

Kehoe 2015⁴¹⁴

Dyspnoea: mean (SD)
 6m follow-up: PDS 16.8 (3.9) vs. NACT 16.3 (3.7)
 12m follow-up: PDS 15.6 (4.3) vs. NACT 18.9 (4.0)
 Overall post-baseline differences between treatment arms: $p=0.049$

Limitations and other comments**Limitations**

Central randomization at EORTC
 Blinding not mentioned (but not realistic for patients and clinicians)
 ITT-analysis, except for quality of life
 Non-inferiority study
 For quality of life, the sample size was reduced. Statistically significant differences were found between the 404 selected patients and the overall population of 670 patients

5.9. Intraperitoneal chemotherapy**Table 93 – Evidence table: SR intraperitoneal versus intravenous chemotherapy**Jaaback K 2011³⁸³**Methods**

Design	SR of RCTs
Source of funding and competing interest	Cochrane review. There was no conflict of interest amongst the authors of the review.
Search date	May 2011
Searched databases	Gynaecological Cancer Review Group's Specialised Register, the Cochrane Central Register of Controlled Trials, EMBASE
Included study designs	RCTs
Number of included studies	9 RCTs, including 2119 women
Statistical analysis	Fixed-effect meta-analysis if it was reasonable to assume that studies were estimating the same underlying effect. If there was clinical heterogeneity or if substantial heterogeneity was detected, random-effects meta-analysis was used. HR were estimated using Parmar's methods if not reported.

Jaaback K 2011 ³⁸³**Patient characteristics**

Eligibility criteria	Standard IV chemotherapy was compared with chemotherapy that included a component of IP administration
Exclusion criteria	The review excluded the following: radio colloids, gene therapy, biologic therapy, radio-isotopes, vascular growth factors, immunomodulating drugs, matrix metalloproteinase inhibitors, radiolabelled monoclonal antibodies
Patient & characteristics	disease Women with a new diagnosis of primary epithelial ovarian cancer, of any FIGO stage, following primary cytoreductive surgery.

Interventions

Intervention group	<p>Chemotherapy that included a component of IP administration</p> <p>Alberts 1996: IV cyclophosphamide (600mg/m²) + IP cisplatin (100mg/m²) repeated every 3 weeks for a total of 6 cycles</p> <p>Gadducci 2000: IV epidox 60mg/m² + IV CTX 600 mg/m² + IP cisplatin 50 mg/m²</p> <p>GOG172: IV paclitaxel 135mg/m² + IP cisplatin 100 mg/m² + IP paclitaxel 60mg/m², repeated every 3 weeks for a total of 6 cycles</p> <p>Kirmani 1994: IP cisplatin 200mg/m² + IP etoposide 350 mg/m²; repeated every 4 weeks for a total of 6 cycles</p> <p>Markman 2001; IV carboplatin (AUC9) for two courses every 28 days, followed 4 weeks later by IV paclitaxel 135mg/m² + IP cisplatin 100mg/m² repeated every three weeks for a total of six cycles</p> <p>Polyzos 1999: IP carboplatin 350 mg/m² + IV cyclophosphamide 600 mg/m²; repeated every 3 to 4 weeks for a total of 6 cycles</p> <p>Yen 2001: IV cyclophosphamide 500mg/m² + IV Adriamycin or epirubicin 50mg/m² + IP cisplatin 100mg/m²; repeated every 3 weeks for a total of 6 cycles</p> <p>Yen 2009: paclitaxel on day 1 with cisplatin or carboplatin IP on day 2; repeated every 3 weeks for 6 cycles</p> <p>Zylberg 1986: IV Adriamycin 20mg X 2 + fluorouracil 500mg X 2 + cisplatin 50mg + vincalucoblastine 10mg + ifosfamide 1g X 2 + IP bleomycin 15mg + cisplatin 50mg + fluorouracil 500mg + Adriamycin 30mg</p>
Control group	Standard IV chemotherapy


Jaaback K 2011 ³⁸³

Albers 1996: IV cyclophosphamide (600mg/m²) + IV cisplatin (100mg/m²) repeated every 3 weeks for a total of 6 cycles
 Gadducci 2000: IV epidox 60mg/m² + IV CTX 600 mg/m² + IV cisplatin 50 mg/m²
 GOG172: IV paclitaxel 135mg/m² + IV cisplatin 75 mg/m², repeated every 3 weeks for a total of 6 cycles
 Kirmani 1994: IV cisplatin 100mg/m² + IV cyclophosphamide 600 mg/m²; repeated every 3 weeks for a total of 6 cycles
 Markman 2001: IV paclitaxel 135 mg/m² + IV cisplatin 75mg/m² repeated every three weeks for six cycles
 Polyzos 1999: IV carboplatin 350 mg/m² + IV cyclophosphamide 600 mg/m²; repeated every 3 to 4 weeks for a total of 6 cycles
 Yen 2001: IV cyclophosphamide 500mg/m² + IV Adriamycin or epirubicin 50mg/m² + IV cisplatin 50mg/m²; repeated every 3 weeks for a total of 6 cycles
 Yen 2009: paclitaxel on day 1 with cisplatin or carboplatin IV on day 2; repeated every 3 weeks for 6 cycles
 Zylberg 1986: IV Adriamycin 35mg X 2 + fluorouracil 750mg X 2 + cisplatin 100mg + vincalucoblastine 10mg + ifosfamide 1g X 2 + bleomycin 15mg

Results

Outcome 1	Primary outcome: Progression-free survival (time to recurrence) HR 0.78; 95%CI 0.70-0.86
Outcome 2	Primary outcome: Overall survival (time to death) HR 0.81; 95%CI 0.72 to 0.90
Outcome 3	Grade 3-4 Adverse effects as measured by any recognised and validated scoring system. It is acknowledged that the frequency of important long-term adverse effects may not be adequately captured by information in (small) RCTs Fever: RR 1.64; 95%CI 1.13-2.38 GI side effects: RR 1.70; 95%CI: 1.28-2.26 Infection: RR 3.34; 95%CI: 2.06-5.43 Pain: RR 7.47; 95%CI: 4.41-12.67 Fatigue: RR 2.32; 95%CI 1.06-5.07 Metabolic adverse events: RR 4.45; 95%CI 2.72-7.26 Hearing loss: RR 0.67; 95%CI 0.46-0.99
Outcome 4	QoL as measured by any scale recognised and validated for cancer care. QoL was only assessed in the GOG 172 trial. More disruption was noted in the IP arm during and shortly after treatment but QoL improved in both arms over time. Only neurotoxicity remained significantly greater in the IP group 12 months after completion of treatment.
Limitations and other comments	
Limitations	Control arm is different from current standard paclitaxel - carboplatin



5.10. First-line weekly (dose dense) chemotherapy

Katsumata 2009, Katsumata 2013, Harano 2014³⁸⁶⁻³⁸⁸

Methods

Design	RCT
Source of funding and competing interest	Bristol-Myers Squibb
Setting	Multicentre study, Japan
Sample size	637 patients enrolled, 631 eligible
Duration and follow-up	Final publications after median follow-up of 76.8 months (IQR 68.9-85.6 months)
Statistical analysis	The cumulative survival curve and median progression-free survival time were estimated by use of the Kaplan-Meier method. Proportions of adverse events were compared between the groups by the use of two-sided χ^2 tests or two-sided Fisher's exact test.

Patient characteristics

Eligibility criteria	Histologically or cytologically proven stage II to IV epithelial ovarian cancer If only cytology available, the following criteria needed to be fulfilled: Diagnosis of adenocarcinoma Abdominal mass mor than 2cm Ca 125/CEA ratio of more than 25 or no evidence of GI cancer Previous chemotherapy was not allowed ECOG preformance status 0-3 Adequate organ function
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Patient & disease characteristics	Median age 57 vs 57 years old ECOG PS 0-1: 91 vs 90% Residual disease \leq 1cm 46% vs 45%
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Interventions

Intervention group	Carboplatin AUC 6 on day 1, paclitaxel 80 mg/m ² 1-h infusion on day 1, 8 and 15, repeated every 3 weeks
Control group	Carboplatin AUC 6 on day 1, paclitaxel 180 mg/m ² 3-h infusion on day 1, repeated every 3 weeks



Katsumata 2009, Katsumata 2013, Harano 2014³⁸⁶⁻³⁸⁸

Results

Progression-free survival (1st outcome)	After a median follow-up of 29 months: HR 0.71; 95%CI 0.58-0.88 (p=0.0015, log-rank test) After median follow-up of 76.8 months for patients with censored data: HR 0.76; 95%CI 0.62-0.91 (p=0.0037)
Overall survival	After a median follow-up of 42 months: HR 0.75; 95%CI 0.57-0.98 (p=0.03) After a median follow-up of 76.8 months for patients with censored data: HR 0.79; 95%CI 0.63-0.99 (p=0.039)
Adverse events	Grade 3-4 anaemia: higher in dose-dense group (p<0.0001) The frequency of neuropathy did not differ between groups.
Quality of life	Response rate at baseline: 63.9% vs 64.1%. Baseline characteristics did not differ significantly. Overall QoL scores: reported scores did not change over time in each group, no statistical difference between two groups. Among subscales, only the FACT-T (taxane) showed significant lower QoL in the dose-dense group

Limitations and other comments

Limitations	Japanese patients only Adverse event analysis only in patients who received at least one cycle of chemotherapy
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Pignata 2014³⁸⁹

Methods

Design	RCT
Source of funding and competing interest	Funding: None All authors declared that they have no competing interests.
Setting	67 institutions in Italy and France
Sample size	822 patients, 12 withdrew consent immediately after randomization and were excluded.
Duration and follow-up	Median follow-up 22.3 months (IQR 16.2-30.9)
Statistical analysis	The Kaplan-Meier product-limit method was used to estimate PFS and OS, curves were compared with the log-rank test. Modified ITT: patients who withdrew their consent immediately after randomization were excluded.



Pignata 2014³⁸⁹

All patients who received chemotherapy at least once were analyzed for adverse events. The worst toxicity grade for every patient was calculated and grades were compared for every type of toxic effect with the exact Wilcoxon-Mann-Whitney test.

The effect of each treatment schedule on every QoL scale was assessed by fitting a linear mixed-effects model, using no within-patient correlation structure among repeated QoL measures

Patient characteristics

Eligibility criteria

Cytological or histological diagnosis of epithelial ovarian, fallopian tube or peritoneal cancer, FIGO stage IC-IV
ECOG PS 0-2
Previous chemotherapy excluded

Patient & disease characteristics

Median age: 59 vs 60 years old
ECOG PS 0 75% vs 74%
No residual disease: 41% vs 41%
Serous disease: 72% vs 67%

Interventions

Intervention group

Carboplatin AUC 2 and paclitaxel 60mg/m² every week for 18 weeks consecutively

Control group

Carboplatin AUC 6 and paclitaxel 175/m² on day 1, every 21 days for 6cycles

Results

Progression-free survival

HR 0.96; 95%CI 0.80-1.16 (p=0.66)
Adjusted HR 0.94; 95%CI 0.78-1.14

Overall survival

HR 1.20; 95%CI 0.90-1.61 (p=0.22)
Adjusted HR 1.21; 95%CI 0.90-1.62

Adverse events

Considering all grades of toxicity, the dose-dense group showed a more favourable pattern for neutropenia, thrombocytopenia, vomiting, hair loss and neuropathy, but a worse pattern for pulmonary toxic effects.

Proportion of women with grade 3-4 toxicity (3-weekly vs once a week):

neutropenia: 50% vs 42%

febrile neutropenia: 3% vs 0.5%

thrombocytopenia: 7% vs 1%

grade 2 or higher neuropathy: 17% vs 6%

**Pignata 2014³⁸⁹**

grade 2 hair loss: 59% vs 29%

Quality of life

Baseline FACT-O/TOI scores were similar between treatment assignments

In all analyses, the treatment-by-time interaction favoured chemotherapy every week ($p < 0.0001$)**Limitations and other comments****Limitations****5.11. Routine CA125 measurement during follow-up****Table 94 – Evidence table: SR routine CA125 measurement during follow-up**Clarke T 2014³⁹⁰**Methods****Design**

SR

Source of funding and competing interest

Department of Health, UK.

NHS Cochrane Collaboration Programme. Grant Scheme CPG-506

Search date

July 2013

Searched databases

Specialised Register of the Cochrane Gynaecological Cancer Group; EMBASE; MEDLINE; CENTRAL

Included study designs

RCTs

Number of included studies

N=1

Statistical analysis

Not applicable

Patient characteristics**Eligibility criteria**

Women of any age diagnosed with primary ovarian cancer of epithelial histological sub-type who have completed primary treatment

Exclusion criteria

Not specifically stated

Patient & disease characteristics

See Rustin 2010

Interventions**Intervention group**

Follow-up strategy following completion of primary treatment



Clarke T 2014³⁹⁰

Control group Other or no follow-up strategy

Results

See Rustin 2010

Limitations and other comments

Comments

Table 95 – Evidence table: RCT routine CA125 measurement during follow-up

Rustin GJ 2010³⁹¹

Methods

Design RCT

Source of funding and competing interest MRC, EORTC

Setting Multicentre, worldwide (59 centres)

Sample size N=529

Duration and follow-up Recruitment: 2/1997-3/2008
Median follow-up from randomisation: 56.9 months

Statistical analysis The primary analysis was the log-rank test, stratified by MRC versus EORTC, applied to compare the Kaplan-Meier survival curves for all time-to-event outcome measures
Cox model sensitivity analyses estimating the treatment effect and adjusting for stratification and prognostic factors were done for overall survival
All p values are two-sided
To adjust for imbalances in follow-up between the two groups, curtailing was used for main analyses of time-to-event outcome measures, by censoring data at 5 years from randomisation for MRC OV05 and 3 years for EORTC 55955. Additional sensitivity analyses were done for uncurtailed data

Patient characteristics

Eligibility criteria Women with histologically confirmed epithelial ovarian, fallopian tube, or serous primary peritoneal cancer (based on local pathology) in complete clinical remission after completion of first-line platinum-based chemotherapy with a normal CA125 concentration

Rustin GJ 2010³⁹¹

Patient & disease characteristics	Median age: 60 vs. 61 years Histology: serous 65% vs. 58% Stage III: 68% vs. 69%
Interventions	
Intervention group	Early treatment on the basis of increased CA125 concentrations (N=265)
Control group	Delayed treatment on the basis of clinical recurrence (N=264)
Results	
Overall survival	HR 0.98 (95%CI 0.80-1.20; p=0.85) Median survival from randomization: 25.7 (23.0-27.9) vs. 27.1 (22.8-30.9) months 2-year survival: 53.7% vs. 54.7% Cox models adjusted for stratification and prognostic factors did not change the overall result
Quality of life	Median time spent with good global health score: 7.2 (95%CI 5.3-9.3) vs. 9.2 months (6.4-10.5) Median time from randomisation to first deterioration in global health score or death: 3.2 (95%CI 2.4-4.3) vs. 5.8 months (4.4-8.5), HR 0.71 (95%CI 0.58-0.88; p=0.002) Subgroup analyses of individual components of the QLQ-C30 subscales showed deterioration in score sooner in the early group than in the delayed group for almost all subscales There was evidence of significant disadvantages for role, emotional, social, and fatigue subscales with early treatment
Time to second-line chemotherapy	Women assigned to early treatment started chemotherapy 4.8 months (95%CI 3.6-5.3) earlier than those allocated delayed treatment
Limitations and other comments	
Limitations	Central randomization at EORTC and MRC Randomisation by minimisation and stratification Blinding of sites and patients ITT-analysis Since the QLQ-C30 questionnaire asks about symptoms only in the previous week, and the forms were completed just before each course of chemotherapy, this method could underestimate any reduction in quality of life due to chemotherapy



Table 98 – GRADE evidence profile: IOTA simple rules

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients pre-test probability of 27%	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with malignant ovarian tumours)	5 studies 1783 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious ²	not serious	none	251 (240 to 257)	⊕⊕⊕⊕ HIGH ¹
False negatives (patients incorrectly classified as not having malignant ovarian tumours)								19 (14 to 30)	
True negatives (patients without malignant ovarian tumours)	5 studies 1783 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	591 (555 to 621)	⊕⊕⊕⊕ HIGH ¹
False positives (patients incorrectly classified as having malignant ovarian tumours)								139 (110 to 175)	



Table 99 – GRADE evidence profile: IOTA LR2

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence						Effect per 1000 patients	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 27%		
True positives (patients with malignant ovarian tumours)	3 studies 1335 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	2	not serious	none	248 (238 to 257)	⊕⊕⊕⊕ HIGH 1
False negatives (patients incorrectly classified as not having malignant ovarian tumours)									22 (14 to 32)	
True negatives (patients without malignant ovarian tumours)	3 studies 1335 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none		606 (562 to 642)	⊕⊕⊕⊕ HIGH 1
False positives (patients incorrectly classified as having malignant ovarian tumours)									124 (88 to 168)	

6.2. Intra-operative frozen section

Results	
Sensitivity	0.90 (95% CI: 0.88 to 0.92)
Specificity	0.99 (95% CI: 0.99 to 1.00)

Results			
Prevalence	25 th percentile: 23.3%	Median: 29.0%	75 th percentile: 37.8%



Table 100 – GRADE evidence profile: intraoperative frozen section

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 23.3%	pre-test probability of 29.0%	pre-test probability of 37.8%	
True positives (patients with malignant ovarian tumours)	37 studies (3096 patients)	cross-sectional (cohort type accuracy study)	serious 1	not serious	not serious 2	not serious	none	210 (205 to 215)	262 (255 to 267)	341 (333 to 349)	⊕⊕⊕○ MODERATE 1
False negatives (patients incorrectly classified as not having malignant ovarian tumours)								23 (18 to 28)	28 (23 to 35)	37 (29 to 45)	
True negatives (patients without malignant ovarian tumours)	37 studies (7431 patients)	cross-sectional (cohort type accuracy study)	serious 1	not serious	not serious	not serious	none	763 (760 to 765)	706 (704 to 708)	619 (616 to 620)	⊕⊕⊕○ MODERATE 1

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients			Test QoE	accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 23.3%	pre-test probability of 29.0%	pre-test probability of 37.8%		
False positives (patients incorrectly classified as having malignant ovarian tumours)								4 (2 to 7)	4 (2 to 6)	3 (2 to 6)		

¹Unclear risk of bias in the majority of studies; most studies retrospective.

²Although there is no perfect overlap of confidence intervals, it was decided not to downgrade, because the various point estimates did not differ substantially.

6.3. Adjuvant chemotherapy

Table 101 – GRADE evidence profile: adjuvant chemotherapy for patients with a (presumed) early stage borderline ovarian tumour

Table 101 GRADE evidence profile: adjuvant chemotherapy for patients with a (presumed) early stage borderline ovarian tumour												
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	with adjuvant chemotherapy	without adjuvant chemotherapy	Relative (95% CI)	Absolute (95% CI)		
Overall survival (follow up: 1 RCT mean 36 (range: 12-84) and other RCT median 147 (range 4 -246) months)												
2	randomised trials	serious ¹	not serious	serious ²	serious ³	none	17	25	Creasman 1982: 0/17 (0%) vs. 0/25 (0%)	0/17	⊕○○○ ○ VERY LOW	CRITICAL
							27	39	Tropé 1993 (study 3): 6/27 (22%) vs. 2/39 (5%), RR 4.33, 95%CI 0.94 to 19.88	6/27		
Disease-free survival (follow up: 1 RCT mean 36 (range: 12-84) and other RCT median 147 (range 4 -246) months)												



2	randomised trials	serious ¹	not serious	serious ²	serious ³	none	17	25	Creasman 1982: 0/17 (0%) vs. 0/25 (0%)	⊕○○○ ○	CRITICAL
							27	39	Tropé 1993 (study 3): 1/27 (4%) vs 0/39 (0%)	VERY LOW	

Quality of life - not reported

-	-	-	-	-	-	-	-	-	-	-	CRITICAL
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Adverse events (follow up: median 147 (range 4 -246) months)

1	randomised trials	serious ¹	not serious	serious ²	serious ³	none	27	39	-Severe septic neutropenia (grade 4): 1/27 (4%) vs. 0/39 (0%) Bone marrow toxicity (grade 3): 1/27 (4%) vs.0/39 (0%)	⊕○○○ VERY LOW	IMPORTANT
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¹Unclear risk of bias for most items

²Chemotherapy regimens used in both RCTs differ from currently used chemotherapy regimens

³Optimal information size not reached

Table 102 – GRADE evidence profile: adjuvant chemotherapy for patients with invasive (presumed) early stage ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adjuvant chemotherapy	without adjuvant chemotherapy	Relative (95% CI)	Absolute (95% CI)		
5-year overall survival												
3	randomised trials	not serious	not serious	not serious	serious ¹	none	506	502	HR 0.71 (0.53 to 0.93)		⊕⊕⊕○ MODERATE	CRITICAL
5-year overall survival - subgroup 'optimal staging'												
2	randomised trials	Serious ⁴	not serious	not serious	very serious ²	none	117	117	HR 1.22 (0.63 to 2.37)		⊕○○○ VERY LOW	CRITICAL
5-year overall survival - subgroup 'suboptimal staging'												
2	randomised trials	not serious	not serious	not serious	serious ¹	none	389	383	HR 0.63 (0.46 to 0.85)		⊕⊕⊕○ MODERATE	CRITICAL



1	randomised trials	not serious	not serious	not serious	serious ¹	none	148	147	HR 0.60 (0.41 to 0.87)	⊕⊕⊕○ MODERATE	CRITICAL
10-year disease-free survival / progression-free survival / recurrence-free survival - subgroup 'low/medium risk'											
1	randomised trials	not serious	not serious	not serious	very serious ¹	none	?	?	HR 0.96 (0.58 to 1.59)	⊕⊕○○ LOW	CRITICAL
10-year disease-free survival / progression-free survival / recurrence-free survival - subgroup 'high risk'											
1	randomised trials	not serious	not serious	not serious	serious ¹	none	?	?	HR 0.52 (0.33 to 0.82)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life - not measured											
-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events - not reported											
-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

MD – mean difference, RR – relative risk

¹Confidence interval crosses clinical decision threshold.

²Both limits of confidence interval cross clinical decision threshold.

³Optimal information size not reached

⁴for one trial only subgroup analysis included (no stratification factor), for the other trial optimal staging status is unsure (no detailed information, post-hoc consideration)

6.4. Laparoscopic surgery in early stage ovarian cancer

As all evidence is derived from non-randomized comparative studies with methodological limitations, we judged to level of evidence to be very low for all outcomes. No formal GRADE profile was drawn up.

6.5. Laparoscopy, PET-CT and MRI to predict end result of cytoreductive surgery

6.5.1. Laparoscopy

Result			Result		
Sensitivity (study 1)	Laparoscopy	0.71 (95% CI: 0.44 to 0.9)	Sensitivity (study 2)	Laparoscopy	0.7 (95% CI: 0.57 to 0.82)
Specificity (study 1)	Laparoscopy	1 (95% CI: 0.9 to 1)	Specificity (study 2)	Laparoscopy	1 (95% CI: 0.94 to 1)



Result
Prevalence 45%

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year pre-test probability of 45%		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Laparoscopy (study 1)	Laparoscopy (study 2)	
True positives (residual disease >1 cm)	2 Studies 74 Patients	observational studies	not serious 1	serious 2	not serious	very serious 3	not serious	320 (198 to 405)	315 (257 to 369)	Very low
False negatives (patients incorrectly classified as not having residual disease >1 cm)								130 (252 to 45)	135 (193 to 81)	
True negatives (patients without residual disease >1 cm)	2 Studies 90 Patients	observational studies	not serious 1	serious 2	not serious	not serious	not serious	550 (495 to 550)	550 (517 to 550)	Moderate
								0 (55 to 0)	0 (33 to 0)	



**False
positives
(patients
incorrectly
classified as
having
residual
disease >1
cm)**

1. Based on judgements of the authors of the original review (Rutten 2014)
2. Applicability concerns regarding patient selection
3. Very wide 95%-Cis

6.5.2. MRI or CT

	Results MRI		Results CT
Sensitivity MRI	0.91 (95% CI: 0.59 to 1)	Sensitivity CT	0.5 (95% CI: 0.12 to 0.88)
Specificity MRI	0.97 (95% CI: 0.87 to 1)	Specificity CT	1 (95% CI: 0.91 to 1)



	Result
Prevalence	18%

Outcome		№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence						Effect per 1000 patients/year		Test accuracy QoE
				Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 18%	MRI	CT	
True positives (patients "unsuccessful cytoreduction")	with	1 Study 17 Patients	observational studies	not serious	serious 1	not serious	very serious 2	not serious	164 (106 to 180)	90 (22 to 158)	Very low	
									74 more TP in MRI			
False negatives (patients incorrectly classified as not having "unsuccessful cytoreduction")									16 (74 to 0)	90 (158 to 22)		
									74 fewer FN in MRI			
True negatives (patients "unsuccessful cytoreduction")	without	1 Study 76 Patients	observational studies	not serious	serious 1	not serious	serious 3	not serious	795 (713 to 820)	820 (746 to 820)	Low	
									25 fewer TN in MRI			
False positives (patients incorrectly classified as having "unsuccessful cytoreduction")									25 (107 to 0)	0 (74 to 0)		
									25 more FP in MRI			



1. High risk of bias due to Patient selection and Reference standard
2. Applicability concerns in all domains. Cut-off for incomplete = 2 cm
3. Very wide 95%-CI

6.5.3. DW-MRI

	Results
Sensitivity	0.75 (95% CI: 0.35 to 0.97)
Specificity	0.96 (95% CI: 0.8 to 1)

	Results
Prevalence	24%

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year pre-test probability of 24%	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with residual disease >1 cm)	1 Study 8 Patients	observational studies	very serious 1 2	very serious 3	not serious	very serious 4	not serious	180 (84 to 233)	Very low
False negatives (patients incorrectly classified as not having residual disease >1 cm)								60 (156 to 7)	
True negatives (patients without residual disease >1 cm)	1 Study 26 Patients	observational studies	very serious 1 2	very serious 3	not serious	very serious 4	not serious	730 (608 to 760)	Very low



**False positives
(patients incorrectly
classified as having
residual disease >1
cm)**

30 (152 to 0)

1. *High risk of bias for Patient selection, Index test and Reference standard*
2. *Post-hoc assessment of optimal index test threshold*
3. *High applicability concerns regarding Patient selection and Index test. Index test not used as add-on to CT.*
4. *Very wide confidence interval*

6.5.4. PET-CT

	Results
Sensitivity	0.66 (95% CI: 0.6 to 0.73)
Specificity	0.88 (95% CI: 0.8 to 0.93)

	Result
Prevalence	65%



Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with residual disease >0 cm)	1 Study 223 Patients	observational studies	serious 1	very serious 2 3 4	not serious	not serious	not serious	429 (390 to 475)	Very low
False negatives (patients incorrectly classified as not having residual disease >0 cm)								221 (260 to 175)	
True negatives (patients without residual disease >0 cm)	1 Study 120 Patients	observational studies	serious 1	very serious 2 3	not serious	serious 4	not serious	308 (280 to 326)	Very low
False positives (patients incorrectly classified as having residual disease >0 cm)								42 (70 to 24)	

1. High risk of bias due to Patient selection and Reference standard

2. Index test not used as add-on to CT

3. Index test also included surgical aggressiveness index

4. Wide CI (esp. broad range of false positives)



6.6. Aim of cytoreductive surgery: no macroscopic disease?

6.6.1. Prognostic value end result of surgery

Table 103 – GRADE evidence profile: prognostic value end result of surgery RD 0.1-1.0 cm compared to microscopic RD

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RD 0.1-1.0 cm	microscopic RD	Relative (95% CI)	Absolute (95% CI)		
Overall survival (HR for death)												
12	observational studies	Not serious 1	not serious	not serious	not serious	publication bias strongly suspected 2	?	?	HR 2.21 (1.97 to 2.47)	-	⊕⊕⊕○ MODERATE	CRITICAL
Progression-free survival (HR for progression)												
53	observational studies	Not serious 1	not serious	not serious	not serious	publication bias strongly suspected 2	?	?	HR 1.91 (1.70 to 2.15)	-	⊕⊕⊕○ MODERATE	CRITICAL

1. Adjusted HRs derived from a prognostic model; probably based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance) However, as findings are consistently confirmed in RCTs (that also included high-risk stage II-III A-B), we decided not to downgrade.

2. Non-reporting of non-significant associations very plausible

3. A sixth study reported that in patients who underwent an UAP those with completely resected disease had better PFS than those with <1 cm ($p < 0.01$)



Table 104 – GRADE evidence profile: prognostic value end result of surgery RD >1 cm compared to microscopic RD

Quality assessment								No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RD >1 cm	microscopic RD	Relative (95% CI)	Absolute (95% CI)			
Overall survival													
8	observational studies	Not serious ¹	not serious	not serious	not serious	publication bias strongly suspected ²	?	?	HR 3.08 (2.44 to 3.88)	-	⊕⊕⊕○ MODERATE	CRITICAL	
Progression-free survival													
4	observational studies	Not serious ¹	not serious	not serious	not serious	publication bias strongly suspected ²	?	?	HR 2.32 (2.05 to 2.62)	-	⊕⊕⊕○ MODERATE	CRITICAL	

1. Adjusted HRs derived from a prognostic model; probably based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance) However, as findings are consistently confirmed in RCTs (that also included high-risk stage II-III A-B), we decided not to downgrade.

2. Non-reporting of non-significant associations very plausible


Table 105 – GRADE evidence profile: prognostic value end result of surgery any RD compared to microscopic RD

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any RD	microscopic RD	Relative (95% CI)	Absolute (95% CI)		
3-year overall survival												
2 ¹	observational studies	Not serious ₂	not serious	not serious	serious ³	publication bias strongly suspected ⁴	?	?	HR 2.03 (1.01 to 4.10)	-	⊕⊕○○ LOW	CRITICAL
3-year progression-free survival												
1 ⁵	observational studies	Not serious ₂	not serious	not serious	not serious	publication bias strongly suspected ⁴	?	?	HR 1.6 (1.3 to 2.1)	-	⊕⊕⊕○ MODERATE	CRITICAL

1. A third study reported that the presence of any macroscopic residual disease after rectosigmoid colectomy was the only significant risk factor for OS ($p=0.003$)

2. Adjusted HRs derived from prognostic models by selecting characteristics on significance, not on including putative confounders in the analysis, irrespective of statistical significance. However, as findings are consistently confirmed in RCTs (that also included high-risk stage II-III A-B), we decided not to downgrade.

3. Wide CI that includes no effect and strong effect

4. Non-reporting of non-significant associations very plausible

5. A second study reported that age greater than 60 years ($p=0.025$), stage IV vs IIIC ($p=0.037$) and any residual disease ($p=0.032$) had an independent association with worse PFS



6.6.2. Effect of (ultra)radical surgery

Table 106 – GRADE evidence profile: effect (ultra)radical surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ultra-radical (extensive) surgery	standard surgery	Relative (95% CI)	Absolute (95% CI)		
Overall survival (follow up: median 43 months)												
1	observational studies	serious ¹²	not serious	not serious	serious ³⁴	none	-/84	-/119	HR 0.56 (0.37 to 0.87)	HR adjusted for age, FIGO stage and residual disease	⊕○○ ○ VERY LOW	CRITICAL
Disease-free survival (follow up: median 49 months)												
1	observational studies	serious ¹²	not serious	serious ⁵	not serious	none	-/124	-/290	HR 1.66 (1.16 to 2.39)	HR for relapse or death, adjusted for FIGO stage, tumour grade, presence of upper abdominal disease, amount of residual disease and	⊕○○ ○ VERY LOW	CRITICAL



										timing of surgery (primary or interval)		
Progression-free survival (follow up: median 43)												
1	observational studies	serious 12	not serious	not serious	serious 34	none	-/84	-/119	HR 0.62 (0.42 to 0.92)	HR adjusted for FIGO stage, tumour grade and residual disease	⊕○○ ○ VERY LOW	CRITICAL
Recurrence rate - not measured												
-	-	-	-	-	-	-	-	see comment	not estimable		-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	see comment	not estimable		-	IMPORTANT
(Loco)regional control - not measured												
-	-	-	-	-	-	-	-	see comment	not estimable		-	IMPORTANT
Adverse events (follow up: median 43-49 months)												
2	observational studies	serious 1	not serious	not serious	serious 4	none			Aletti 2006: Perioperative mortality (death within 2 weeks following surgery): 0 vs 3 women (not		⊕○○ ○ VERY LOW	IMPORTANT



adjusted for
baseline
imbalances)

Significant
postoperative
morbidity 32/84
(38.1%) vs 14/119
(11.8%)

Luyckx 2012:

Postoperative death
within 30 days 1/84
(1.2%) vs 0/119
(0%)

“Patients who
underwent radical
surgery had
significantly longer
operative time,
larger estimated
blood loss, more
blood transfusions,
longer stay in the
intensive care unit,
and more
lymphocysts than
those who
underwent simple
surgery.”

MD – mean difference, RR – relative risk

1. Confounding by indication

2. Adjusted HRs derived from a prognostic model; probably based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance).

3. Wide confidence interval

4. OIS not reached

5. Sample included a mixture of primary and interval debulking surgery

6.7. Neo-adjuvant chemotherapy and interval debulking versus upfront surgery

Table 107 – GRADE evidence profile: primary debulking versus neo-adjuvant chemotherapy

Table 107 GRADE evidence profile: primary debulking versus neo-adjuvant chemotherapy														
Quality assessment									No of events/patients		Effect		Quality	Importance
No of studies	Design	Risk bias	of inconsistency	Inconsistency	Indirectness	Imprecision	Other considerations	Primary debulking	Neo-adjuvant platinum-based chemotherapy	Relative (95% CI)	Absolute			
Death (overall survival)														
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	HR 0.93 (0.81 to 1.06)	-	⊕⊕⊕⊕ HIGH	Critical	
Death (overall survival): subanalysis stage III ⁹														
2	randomised trials	no serious risk of bias	serious ¹⁰	no serious indirectness	no serious imprecision	none	-	-	-	HR 0.97 (0.78 to 1.20)	-	⊕⊕⊕O MODE RATE	Critical	
Death (overall survival): subanalysis stage IV ⁹														
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	HR 0.80 (0.77 to 1.04)	-	⊕⊕⊕⊕ HIGH	Critical	
Death (overall survival): subanalysis metastatic tumour load 0-5 cm ⁹														



Quality assessment									No of events/patients		Effect		Quality	Importance
No of studies	Design	Risk bias	of	Inconsistency	Indirectness	Imprecision	Other considerations		Primary debulking	Neo-adjuvant platinum-based chemotherapy	Relative (95% CI)	Absolute		
2	randomised trials	serious ^{1,2}		serious ³	no serious indirectness	serious ⁴	none		216	213	-	MD 3.79 lower (12.16 lower to 4.59 higher)	⊕○○○ VERY LOW	Important

QLQ-C30: global health/QOL at 12m (Better indicated by higher values)

2	randomised trials	serious ^{1,2}		serious ⁷	no serious indirectness	no serious imprecision ⁸	none		142	133	-	MD 1.80 lower (9.92 lower to 6.32 higher)	⊕⊕○○ LOW	Important
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QLQ-C30: pain at 6m (Better indicated by higher values)

1	randomised trials	serious ^{1,2}		no serious inconsistency	no serious indirectness	serious ⁴	none		113	99	-	MD 3.6 higher (6.66 lower to 13.86 higher)	⊕⊕○○ LOW	Important
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QLQ-C30: pain at 12m (Better indicated by higher values)



Quality assessment										No of events/patients		Effect		Quality	Importance
No of studies	Design	Risk bias	of	Inconsistency	Indirectness	Imprecision	Other considerations	Primary debulking	Neo-adjuvant platinum-based chemotherapy	Relative (95% CI)	Absolute				
2	randomised trials	serious ¹	no	serious inconsistency	no serious indirectness	no serious imprecision	none	41/565 (7.3%)	11/541 (2.0%)	RR 3.42 (1.53 to 7.66)	49 more per 1000 (from 11 to 135 more)	⊕⊕⊕⊕O	MODE RATE		Important
Gastrointestinal fistula															
2	randomised trials	serious ¹	no	serious inconsistency	no serious indirectness	very serious ⁶	none	5/565 (0.88%)	2/541 (0.37%)	RR 2.38 (0.47 to 12.12)	5 more per 1000 (from 2 fewer to 41 more)	⊕○○○	VERY LOW		Important
Urinary fistula															
2	randomised trials	serious ¹	no	serious inconsistency	no serious indirectness	very serious ⁶	none	2/565 (0.35%)	2/541 (0.37%)	RR 0.94 (0.13 to 6.67)	0 fewer per 1000 (from 3 fewer to 21 more)	⊕○○○	VERY LOW		Important



¹ No blinding.

² No intention-to-treat analysis.

³ $I^2 = 66\%$.

⁴ CI includes MID.

⁵ $I^2 = 84\%$.

⁶ Broad CI that includes appreciable benefit and harm.

⁷ $I^2 = 46\%$.

⁸ CI includes 0, but does not cross MID of 10 points.

⁹ Predefined groups.

¹⁰ I^2 53%, not only IIIC in Kehoe 2015..

¹¹ I^2 84%, opposite results.



6.8. Intraperitoneal chemotherapy

Quality assessment								No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intra-peritoneal chemotherapy	Intravenous chemotherapy	Relative (95%CI)	Absolute			
Progression-free survival													
5	RCTs	no serious risk of bias	no serious inconsistency	serious ¹	serious ²	none		-	HR 0.78 (0.70-0.86)		⊕⊕⊕⊕ LOW	CRITICAL	
Overall survival													
8	RCTs	no serious risk of bias	no serious inconsistency	serious ¹	serious ²	none	-	-	HR 0.81 (0.72-0.90)	-	⊕⊕⊕⊕ LOW	IMPORTANT	
Grade 3-4 gastrointestinal side effects													
5	RCTs	no serious risk of bias	no serious inconsistency	serious ¹	no serious imprecision	none	230/660 (34.8%)	131/679 (19.3%)	1.70 (1.28-2.26)	170 more per 1000 (from 68 more to 307 more)-	⊕⊕⊕⊕ MODE RATE	IMPORTANT	
Grade 3-4 fatigue													
3	RCTs	no serious risk of bias	no serious inconsistency	serious ¹	serious ²	none	88/582 (15.1%)	44/589 (7.5%)	2.32 (1.06-5.07)	57 more per 1000 (from 3 more to 175 more)	⊕⊕⊕⊕ LOW	IMPORTANT	



Grade 3-4 neurologic adverse events

6	RCTs	no serious risk of bias	serious ³	serious ¹	serious ⁴	none	114/910 (12.5%)	106/955 (11.01%)	1.15 (0.67-1.97)	13 more per 1000 (from 28 fewer to 82 more)	IMPORTANT
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Quality of Life

1	RCTs	no serious risk of bias	no serious inconsistency	serious ¹	serious ²	none	-	-	-	⊕⊕⊕⊕ LOW	IMPORTANT
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¹ Comparator not current standard chemotherapy

² Confidence interval includes minimal clinical decision threshold

³ $I^2=69\%$, visual heterogeneity on forest plot

⁴ Confidence interval includes both benefit and harm



6.9. First-line weekly (dose dense) chemotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dose-dense chemotherapy (TC)	3-weekly TC	Relative (95% CI)	Absolute		
Progression-free survival												
2	randomised trials	no serious risk of bias	very serious ¹	no serious indirectness	serious ²	none	718	723	HR 0.83 (0.62-1.11)	-	⊕○○○ VERY LOW	CRITICAL
Overall survival												
2	randomised trials	no serious risk of bias	very serious ¹	no serious indirectness	serious ²	none	718	723	HR 0.95 (0.60-1.50)	-	⊕○○○ VERY LOW	IMPORTANT

¹ Serious unexplained heterogeneity, contradictory results.

² Confidence includes both appreciable benefit and harm.



6.10. Routine CA125 measurement during follow-up

Table 108 – GRADE evidence profile: routine CA125 measurements during follow-up

Quality assessment										No of patients		Effect		Quality	Importance
No of studies	Design	Risk bias	of inconsistency	Inconsistency	Indirectness	Imprecision	Other considerations	Early treatment	Delayed treatment	Relative (95% CI)	Absolute				
Overall survival (follow-up median 56.9 months)															
1	randomised trials	no serious risk of bias	no inconsistency	serious inconsistency	no serious indirectness	very serious ¹	none	79/265 (29.8%) ²	80/264 (30.3%) ²	HR 0.98 (0.80 to 1.20)	-	⊕⊕○○	LOW		
Time to second-line chemotherapy (follow-up median 56.9 months)															
1	randomised trials	no serious risk of bias	no inconsistency	serious inconsistency	no serious indirectness	no serious imprecision	none	11/265 (4.2%) ³	31/264 (11.7%) ³	HR 0.29 (0.24 to 0.35)	-	⊕⊕⊕⊕	HIGH		
Time to third-line treatment or death (follow-up median 56.9 months)															
1	randomised trials	no serious risk of bias	no inconsistency	serious inconsistency	no serious indirectness	no serious imprecision	none	Median 12.5 months	Median 17.1 months	HR 0.69 (0.57 to 0.83)	-	⊕⊕⊕⊕	HIGH		
Time to first deterioration in good global health score or death (follow-up median 56.9 months)															
1	randomised trials	serious ⁴	no inconsistency	serious inconsistency	no serious indirectness	no serious imprecision	none	Median 3.2 months	Median 5.8 months	HR 0.71 (0.58 to 0.88)	-	⊕⊕⊕○	MODERATE		

¹ CI includes benefit and harm.

² Proportion survivors at data locking.

³ Proportion of patients not started with second-line chemotherapy at data locking.

⁴ Point estimates and 95% CIs (i.e. adjusted hazard ratios) did not tally with corresponding P values (calculated with Kaplan-Meier, thus unadjusted) for time to first deterioration in QoL score or death for many of the individual sub-scales of EORTCQLQ-C30 questionnaire (Table 4 in trial report). For example, for the emotional sub-scale in the functional QoL category the upper 95% CI was 1.02 and the P value was 0.02. Similarly, several sub-scale factors appeared to have a vastly decreased P value from what might be expected given the point and CI estimates. These discrepancies at least suggest prognostic imbalances between the treatment groups.



7. FOREST PLOTS

7.1. Intra-operative frozen section

Figure 33 – Paired forest plot of sensitivity and specificity of frozen section: malignant versus borderline or benign ovarian tumours

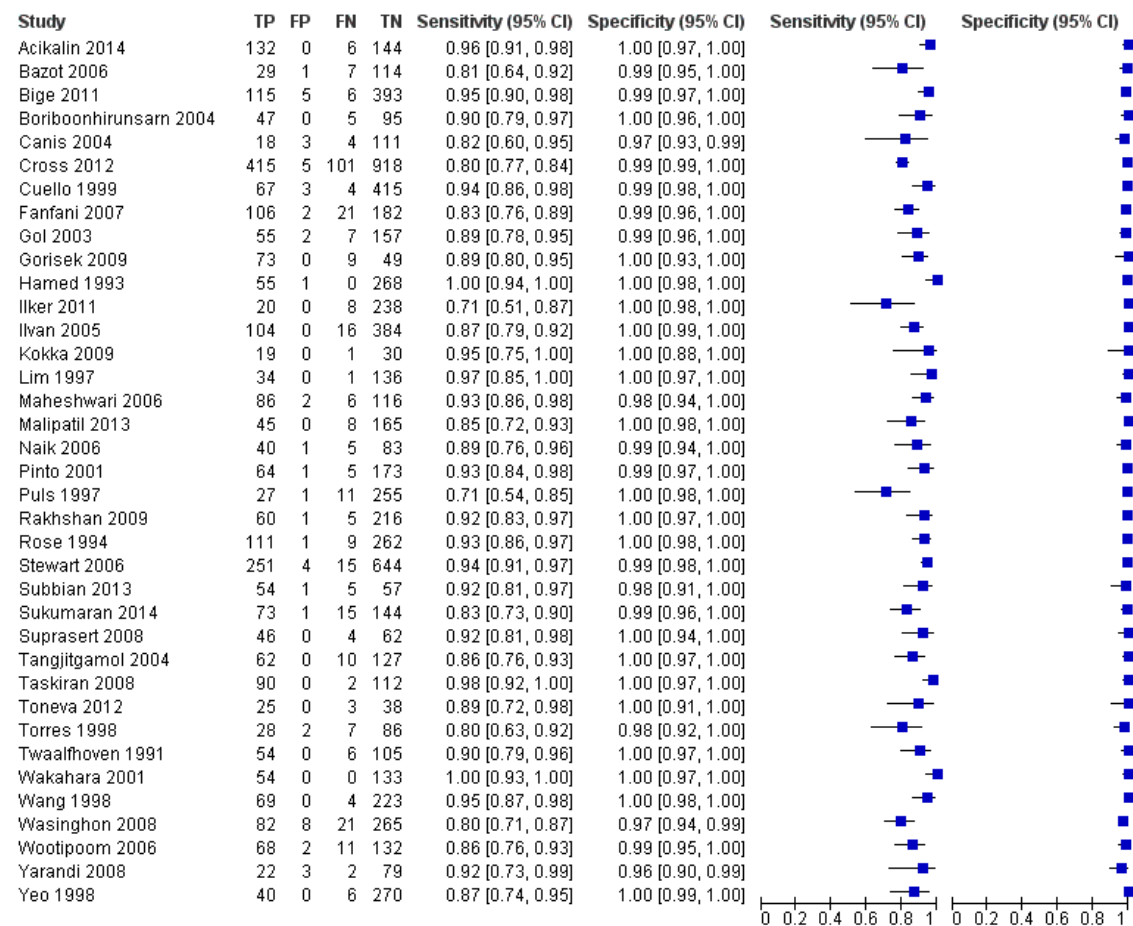




Figure 34 – ROC plot of individual and pooled sensitivity and specificity of frozen section: malignant versus borderline or benign ovarian tumours

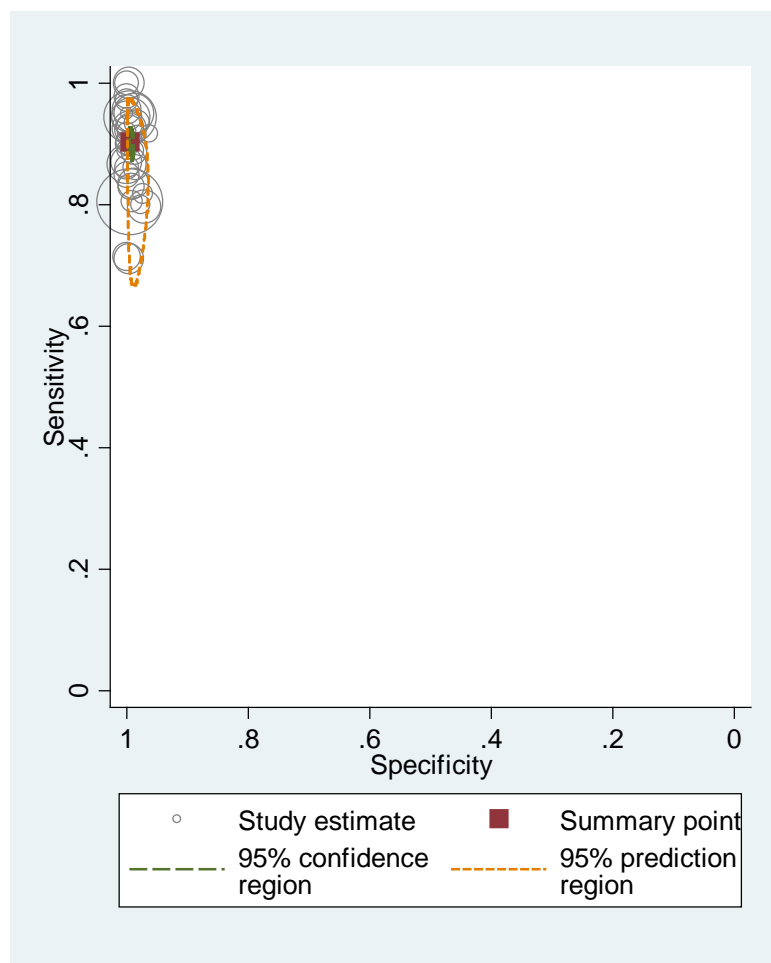




Figure 35 – Paired forest plot of sensitivity and specificity of frozen section: malignant or borderline ovarian tumours versus benign tumours

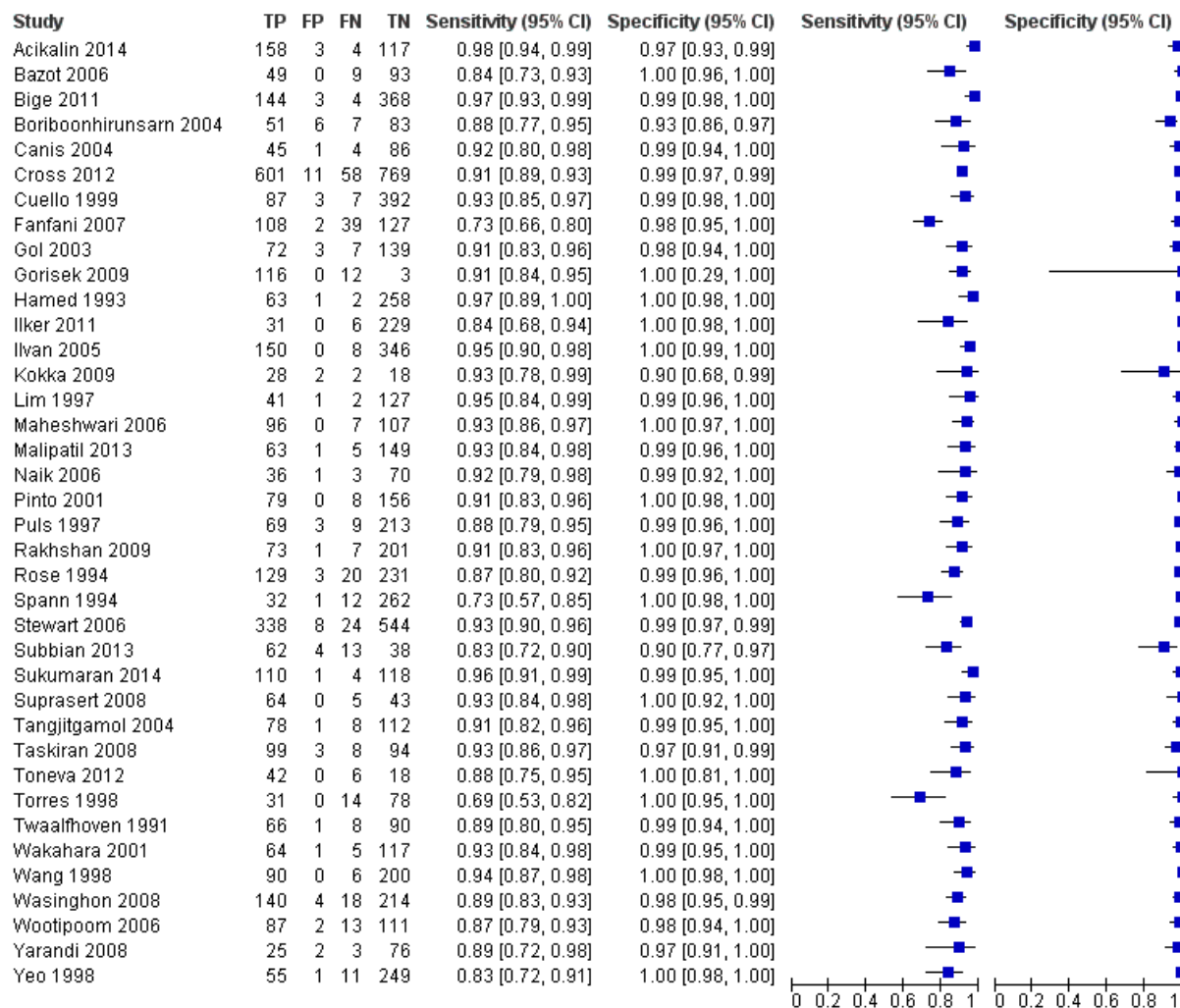
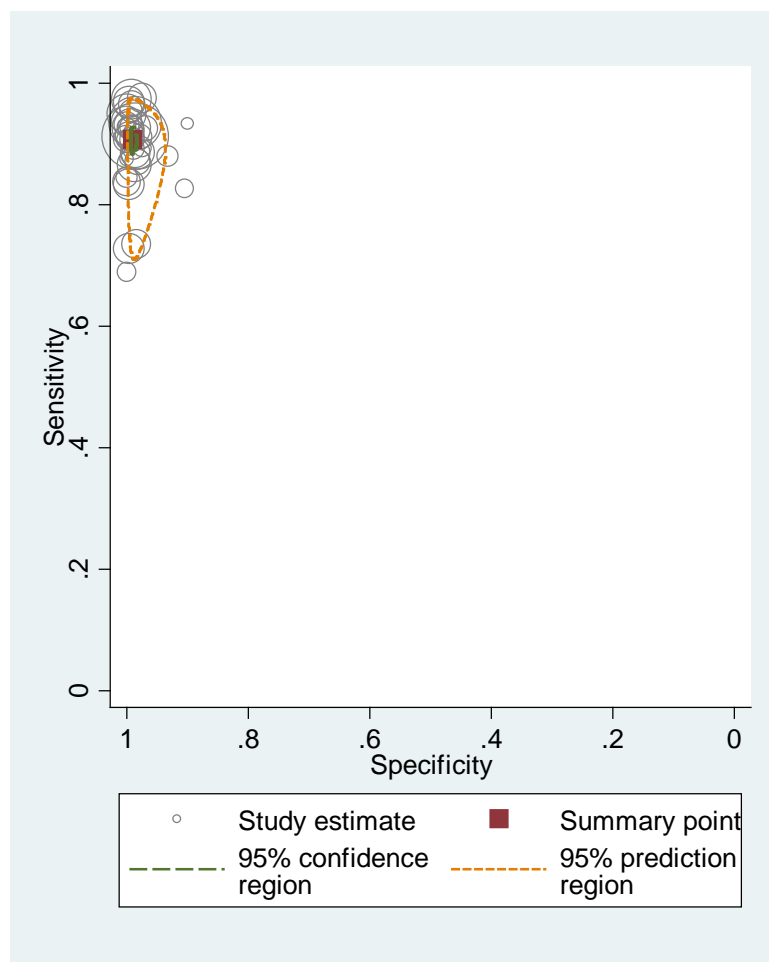




Figure 36 – ROC plot of individual and pooled sensitivity and specificity of frozen section: malignant or borderline versus benign ovarian tumours





7.2. Aim of cytoreductive surgery: no macroscopic disease?

Figure 37 – Prognostic value end result surgery: forest plot overall survival RD 0.1-1.0 cm vs. microscopic RD

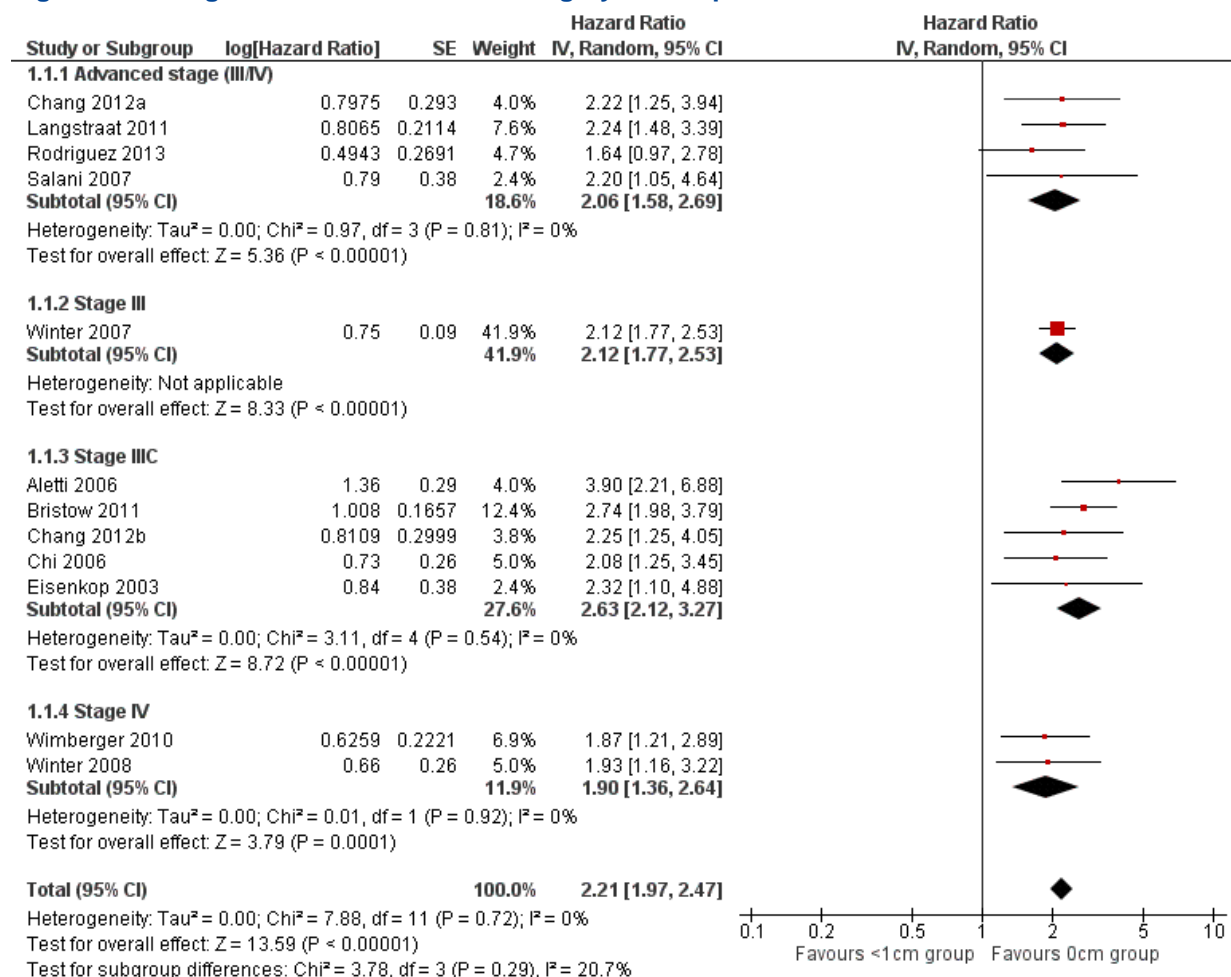


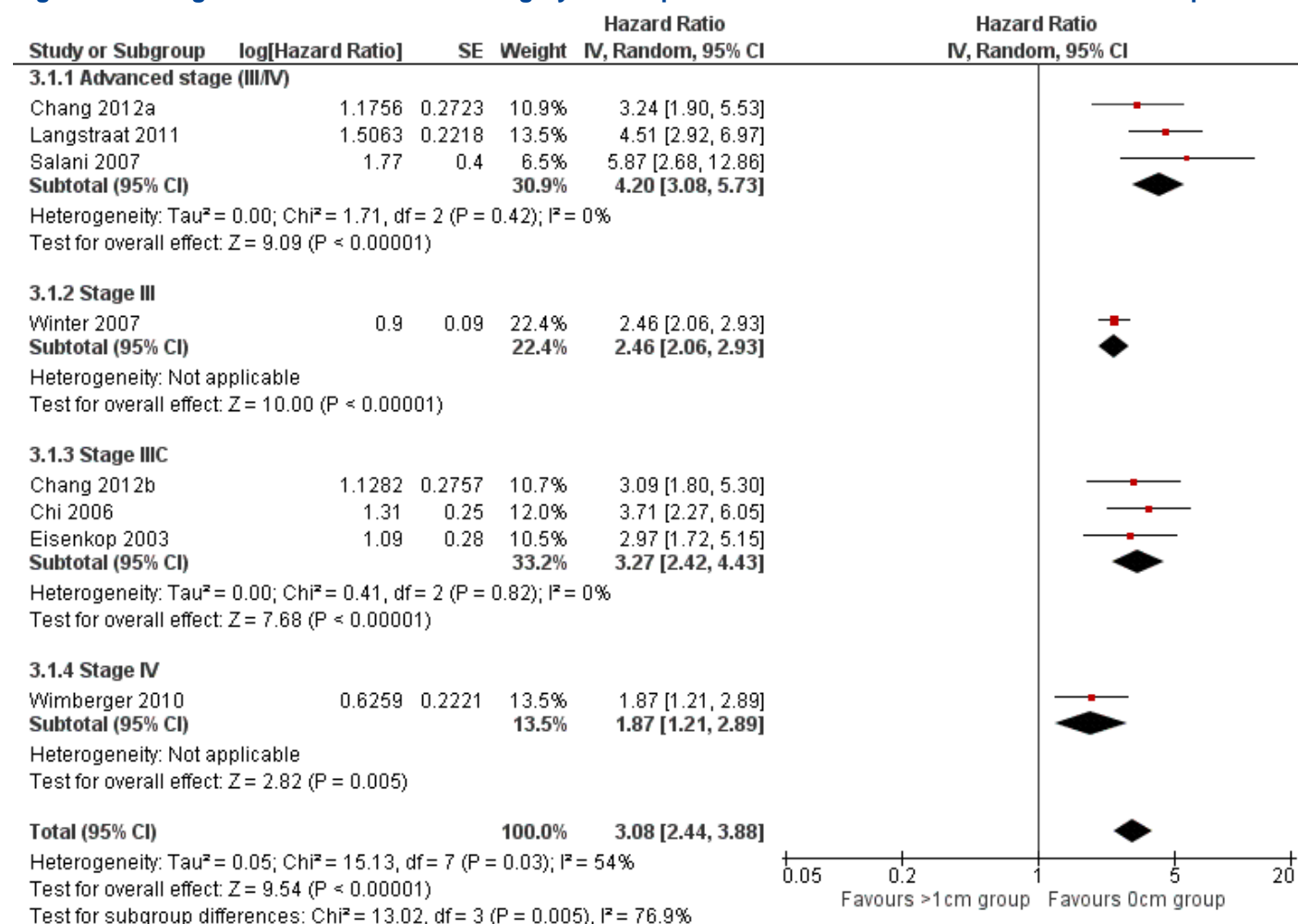

Figure 38 – Prognostic value end result surgery: forest plot overall survival RD >1.0 cm vs. microscopic RD




Figure 39 – Prognostic value end result surgery: forest plot overall survival RD >0 cm vs. microscopic RD (0 cm)

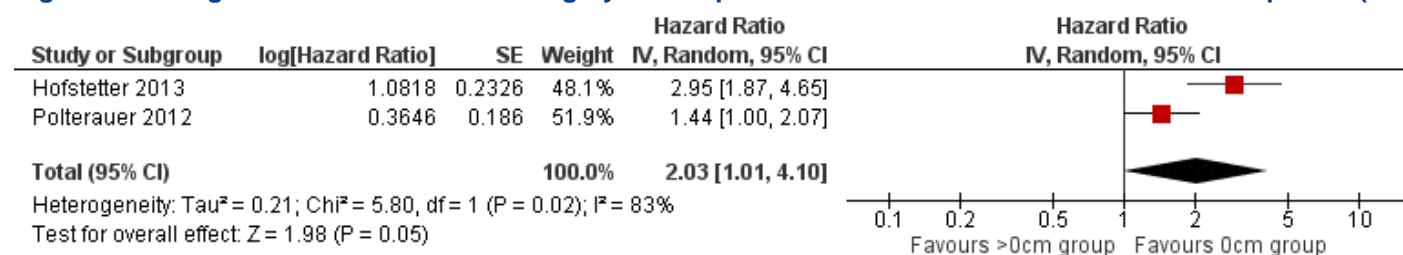


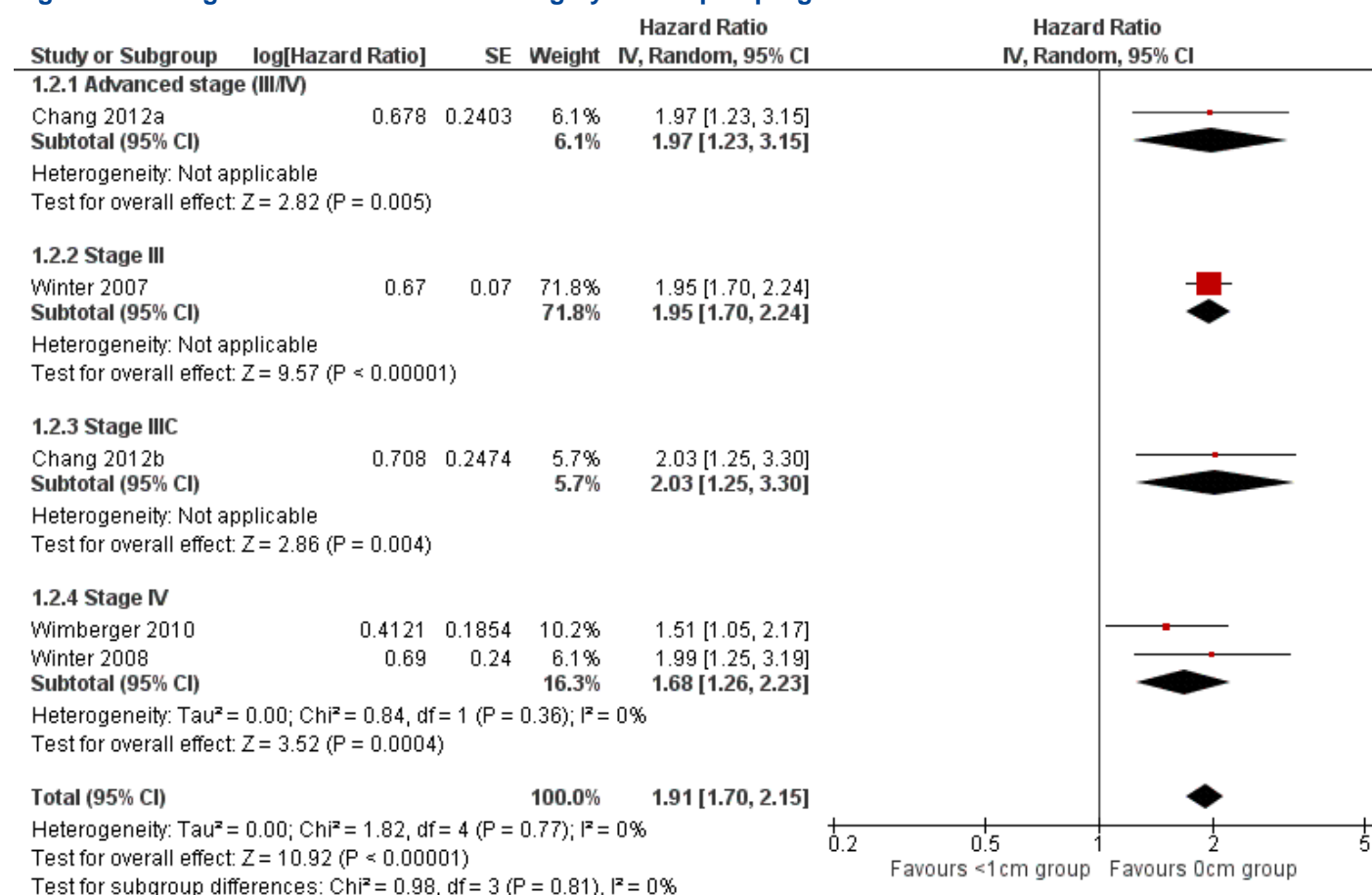
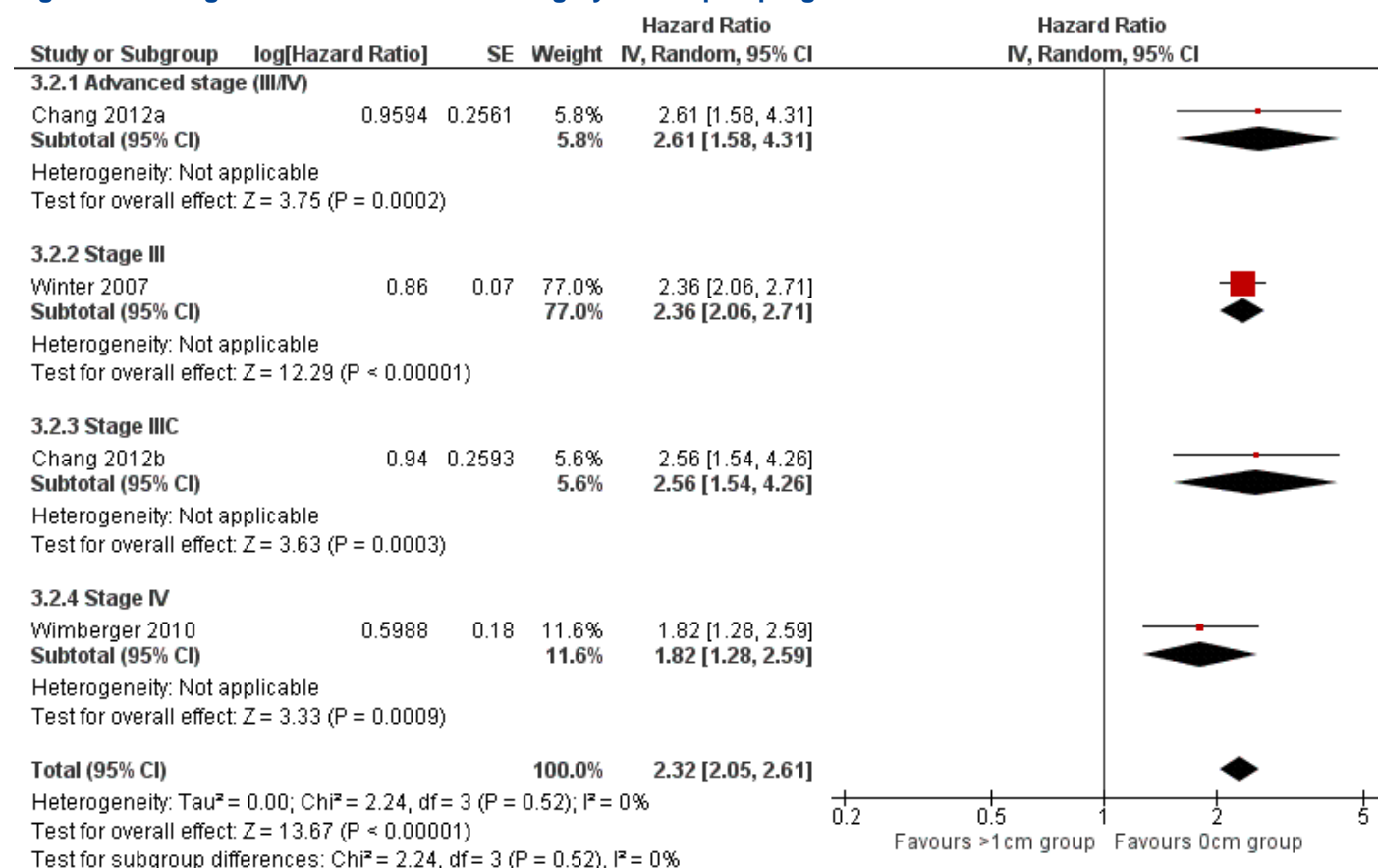

Figure 40 – Prognostic value end result surgery: forest plot progression-free survival RD 0.1-1.0 cm vs. microscopic RD




Figure 41 – Prognostic value end result surgery: forest plot progression-free survival RD >1.0 cm vs. microscopic RD





7.3. Neoadjuvant chemotherapy and interval debulking versus upfront surgery

Figure 42 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot overall survival

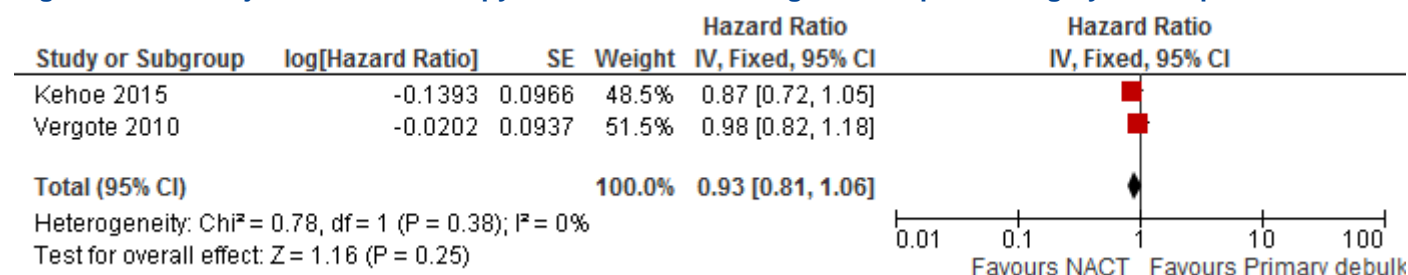


Figure 43 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot progression-free survival

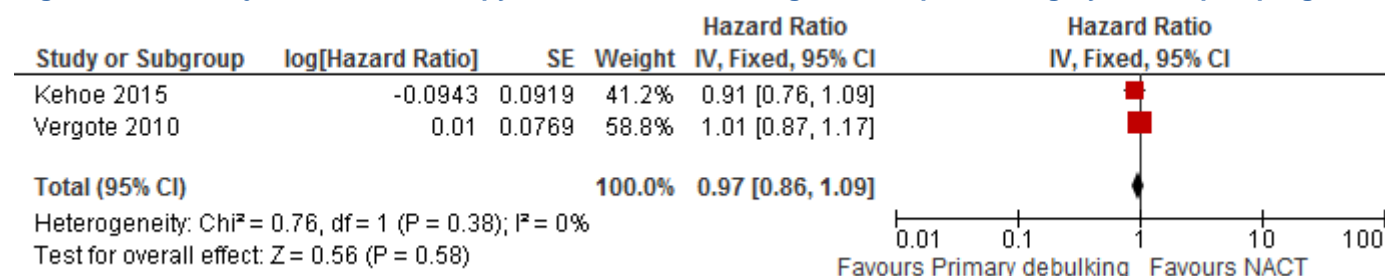


Figure 44 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot QLQ-C30, global health/QOL at 6 months

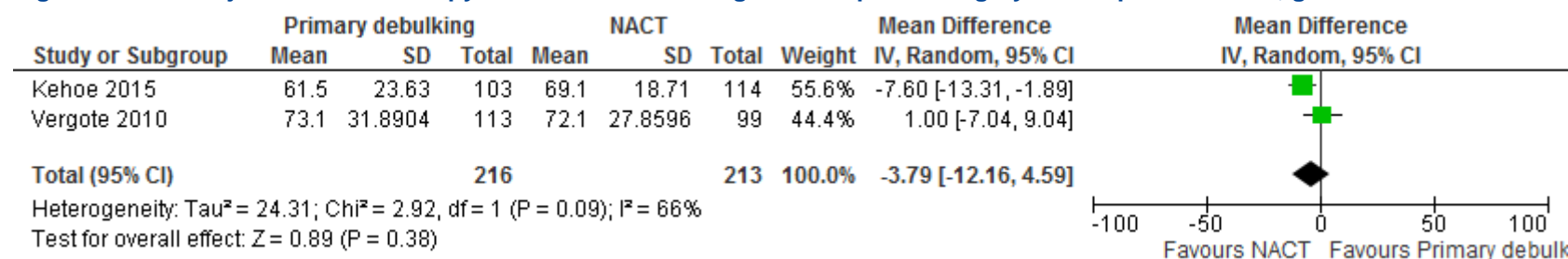




Figure 45 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot QLQ-C30, global health/QOL at 12 months

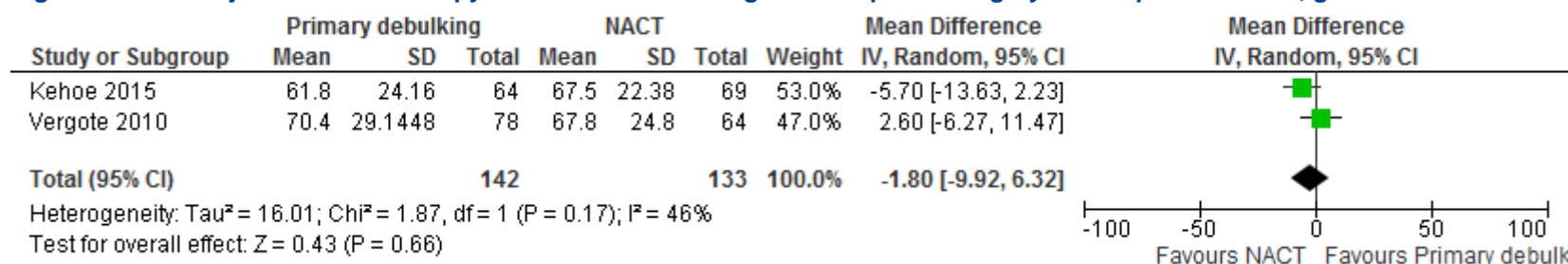


Figure 46 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot postoperative death

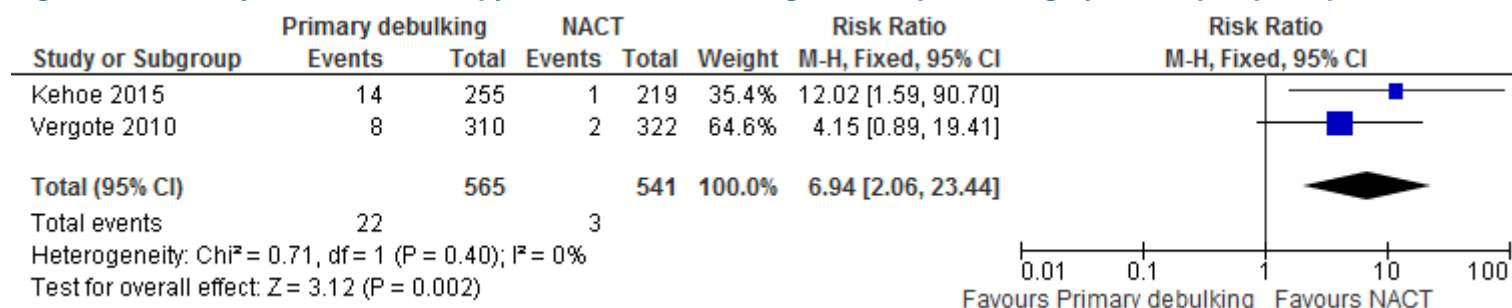


Figure 47 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot postoperative haemorrhage grade 3-4

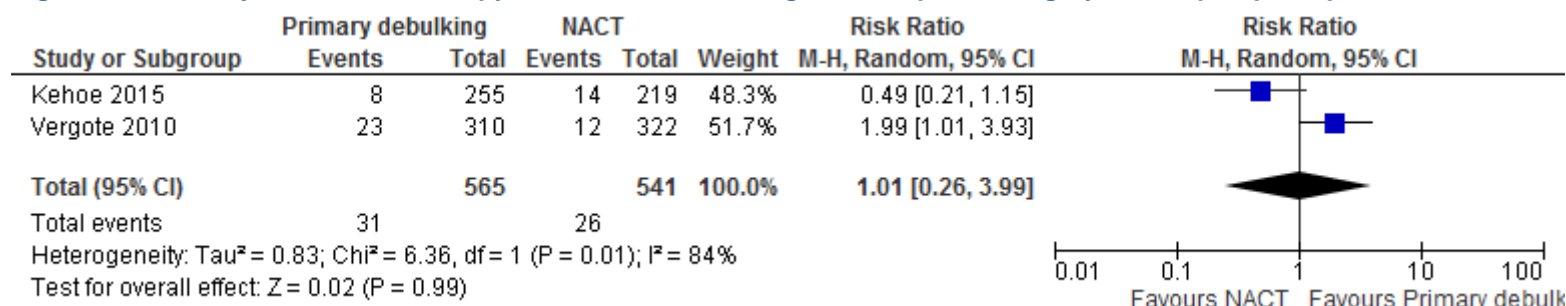




Figure 48 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot postoperative venous complications grade 3-4

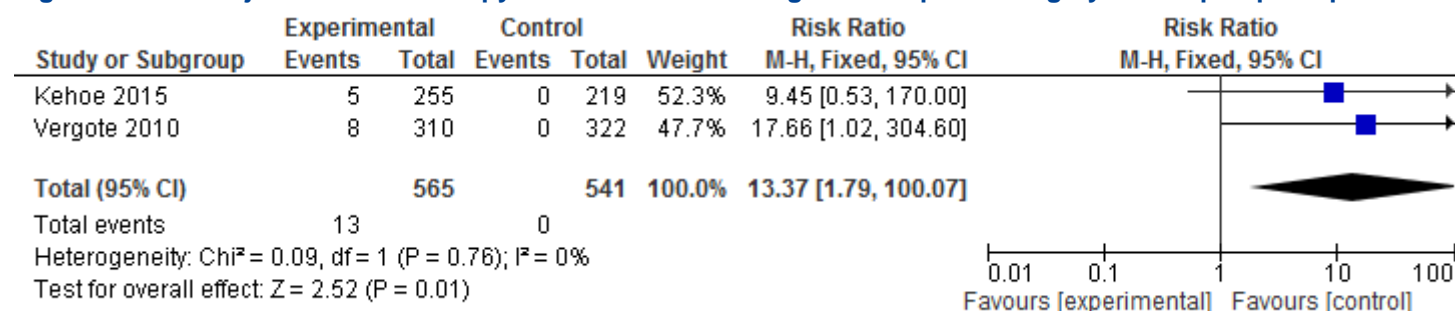


Figure 49 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot postoperative infections grade 3-4

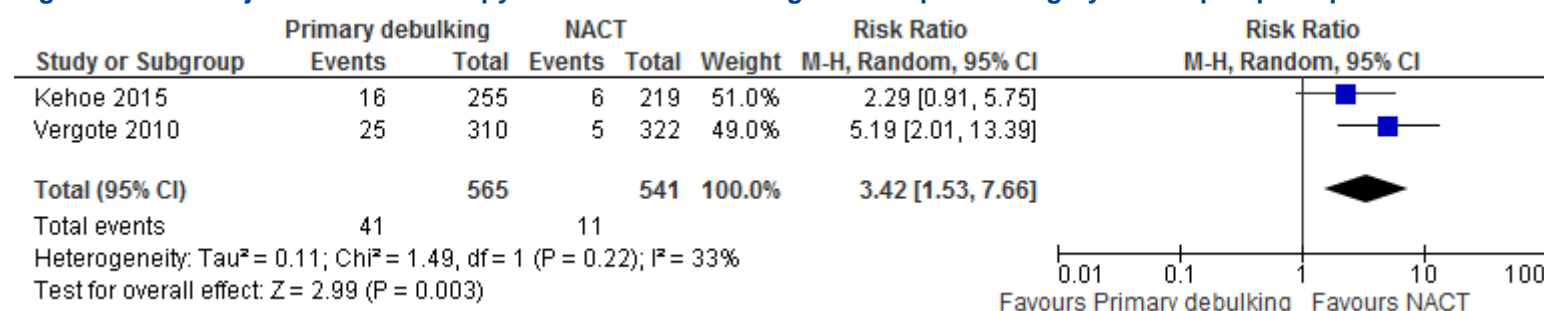


Figure 50 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot gastrointestinal fistula

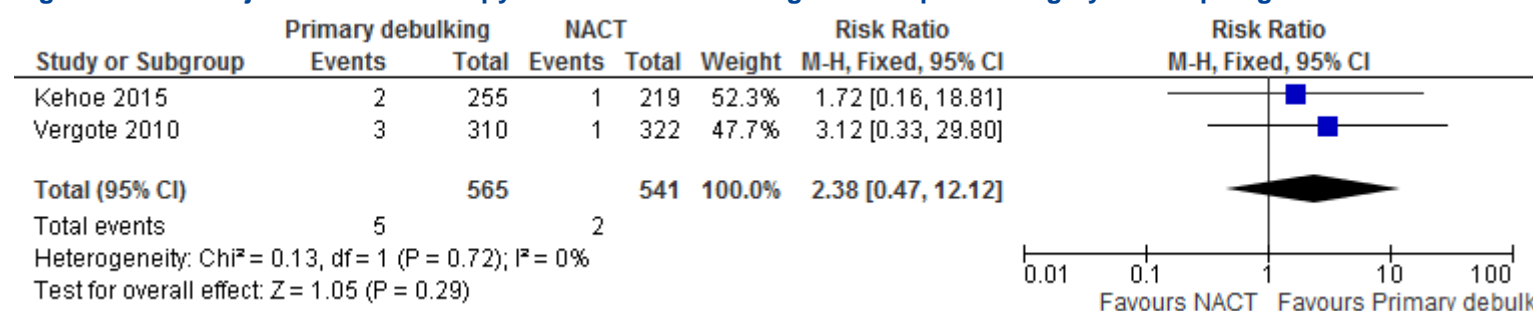
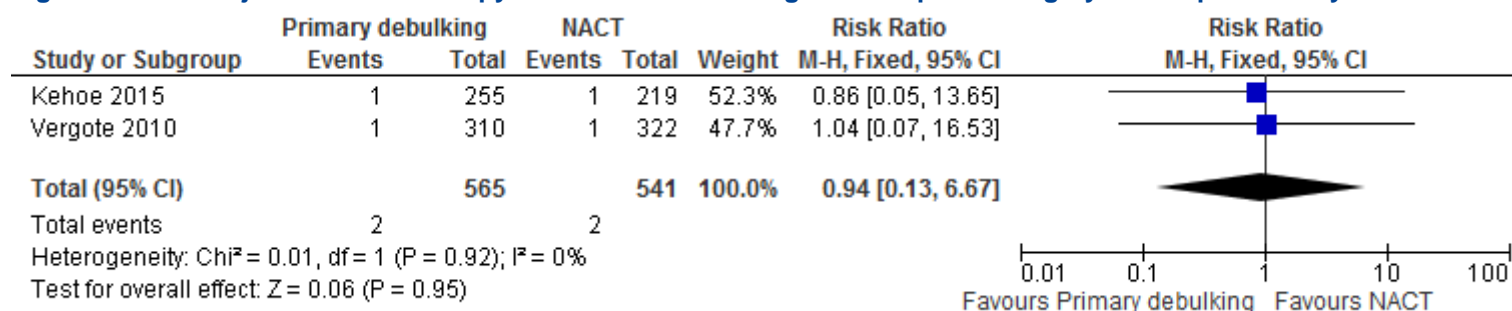




Figure 51 – Neoadjuvant chemotherapy and interval debulking versus upfront surgery: forest plot urinary fistula



7.4. First-line weekly (dose dense) chemotherapy

Figure 52 – Dose-dense chemotherapy: forest plot progression-free survival

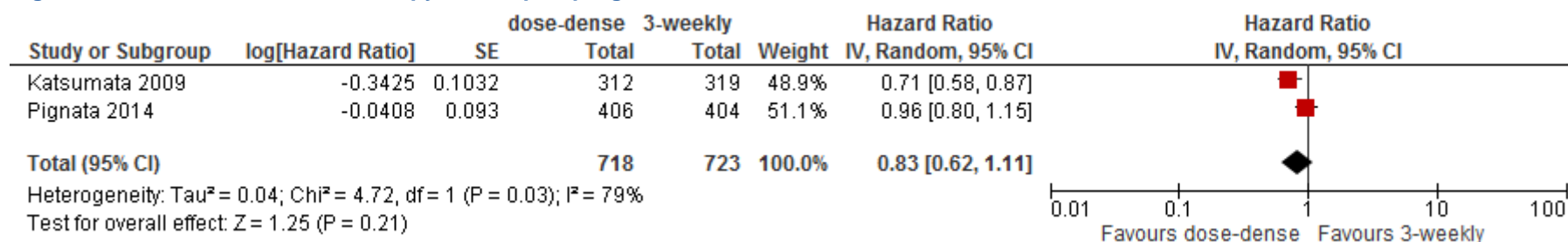
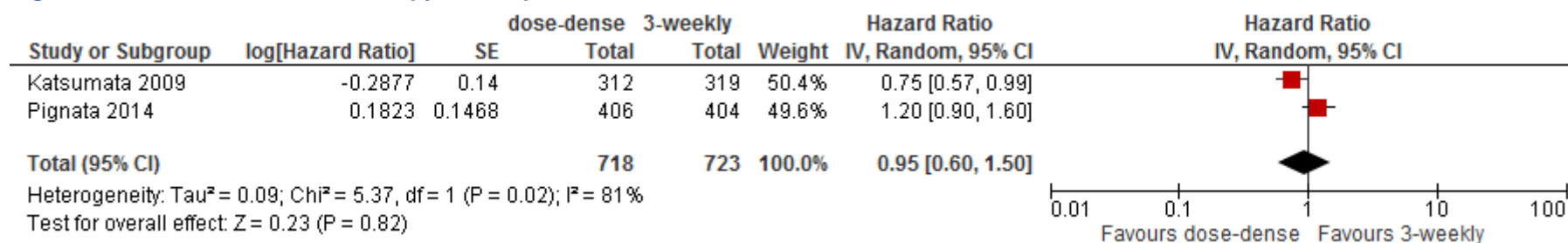


Figure 53 – Dose-dense chemotherapy: forest plot overall survival





8. EXTERNAL REVIEW

8.1. Stakeholder review

Item	Recommendation(s)	SH1	SH2	SH3	SH4	SH5	Min	Max	Med	Mean	% 4-5	Comments	Action
Early stage disease													
Preoperative assessment pelvic mass	Assess a pelvic mass preoperatively using IOTA simple rules, IOTA logistic regression 2 or the ADNEX model to inform clinical decisions regarding surgery (surgery versus expectant management, laparoscopy versus laparotomy, surgery in specialized centre or not). If (borderline) malignancy is suspected, the patient should be discussed preoperatively in the multidisciplinary board in the presence of at least one representative of the Reference Centre.	5	NA	NA	5	5	5	5	5	5	100%		Slightly rephrased
Intra-operative frozen section	Perform intraoperative frozen section to guide decisions during surgery e.g. regarding staging procedures for presumed early stage (borderline) ovarian cancer.	5	5	NA	5	4	4	5	4,5	4,5	100%	SH5: Unless preop biopsy or cytology	None
Lymphadenectomy	Do not perform lymphadenectomy for borderline ovarian tumours.	5	5	5	5	5	5	5	5	5	100%		None
	Consider omitting lymphadenectomy in well differentiated stage I ovarian tumours and stage I mucinous tumours of the expansile type.	5	4	4	5	3	3	5	4	4	80%	SH2: different grading systems according to histological tumour type should be explained in the guideline	None Grading systems explained
Adjuvant chemotherapy	Do not offer adjuvant chemotherapy to patients with an early stage borderline ovarian tumour.	5	5	5	5	5	5	5	5	5	100%		None
	Do not offer adjuvant chemotherapy to patients with an early stage micro-invasive ovarian tumour.	5	5	5	5	4	4	5	5	4,6	100%		None
	Do not offer adjuvant chemotherapy to low risk early stage (FIGO stage IA Grade 1) ovarian cancer.	5	4	5	5	3	3	5	5	4,2	80%	SH2: different grading systems according to histological tumour type should be explained in the guideline	None Grading systems explained
	Offer platinum-based adjuvant chemotherapy to fit patients with medium risk or high risk early stage ovarian cancer, whether or not the tumour is optimally staged.	5	2	4	5	5	2	5	5	4,4	80%	SH2: the footnote \$ should be corrected: stage IA grade 3 instead of grade 1-2-3 SH3: High risk early stage ovarian cancers are not correctly indicated in the footnote to the recommendation	Footnotes corrected
Laparoscopic surgery	Do not routinely consider laparoscopic surgery for (presumed) early stage ovarian cancer. Laparoscopy can be considered if the chance of invasive disease is considered to be low preoperatively and the tumour is small (< 6cm), for restaging after laparotomy or for restaging of tumours at low risk for peritoneal spread.	4	NA	4	5	4	4	5	4	4,4	100%		Split in two recommendations with slight rephrasing



Item	Recommendation(s)	SH1	SH2	SH3	SH4	SH5	Min	Max	Med	Mean	% 4-5	Comments	Action
Advanced stage disease													
Laparoscopy, PET-CT and MRI	In addition to initial staging CT scan, laparoscopy or DW-MRI can be considered for stage III or IV ovarian cancer, to assess the resectability of the abdominal tumour.	4	NA	4	5	5	4	5	5	4,8	100%		None
	Results of a staging PET/CT should not be used to assess resectability of the abdominal tumour.	5	NA	4	5	3	3	5	4	4	75%	SH5: What about recurrent disease? (Anticancer Res. 2008 Jul-Aug;28(4C):2303-8. PET-CT in recurrent ovarian cancer: impact on treatment planning. Lenhard MS1, Burges A, Johnson TR, Stieber P, Kümper C, Ditsch N, Linke R, Friese	None Recurrence is out of scope
Cytoreductive surgery	The aim of cytoreductive surgery for ovarian cancer (upfront or interval debulking surgery) should be to remove all macroscopic tumour.	4	5	5	5	5	4	5	5	4,8	100%		None
Neoadjuvant chemotherapy and interval debulking	Consider neoadjuvant chemotherapy and interval debulking surgery in patients with (biopsy proven) FIGO stage IIIC or IV cancer, especially in case of stage IV disease, high tumour load (maximum metastatic diameter > 5cm) or expected high morbidity. Primary debulking surgery is preferable if tumour load is more limited and the tumour is more easily resectable.	5	5	5	5	5	5	5	5	5	100%		None
Intra-peritoneal chemotherapy	Do not routinely offer first-line intra-peritoneal chemotherapy to women with advanced-stage ovarian cancer.	4	NA	2	4	5	2	5	4	4	75%		None More explanation in text on why a negative recommendation was chosen
First-line dose-dense chemotherapy	Both weekly and 3-weekly administration of paclitaxel with 3-weekly carboplatin can be considered as first-line chemotherapy for advanced ovarian cancer.	5	NA	4	4	4	4	4	4	4	100%	SH3: Comments leading to this recommendation are not clearly formulated in the guidelines since one study compared weekly paclitaxel vs 3-weekly paclitaxel alone whereas the other study compared weekly vs 3-weekly administration of both paclitaxel and carboplatin. Only the first study showed some possible advantages SH5: Prefer 3w	None Explaining text adapted
Follow-up													
Routine CA125 measurements	Do not offer chemotherapy for recurrent ovarian cancer based on raised Ca 125 alone, in the absence of symptoms.	5	5	5	5	4	4	5	5	4,6	100%		None



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