Laparoscopy versus laparotomy for FIGO Stage I ovarian cancer (Protocol)

Medeiros LR, Rosa DD, Bozzetti MC, Edelweiss MI, Stein AT, Pohlmann P, Zelmanowicz A, Ethur AB, Zanini RR

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
The objective of this review will be to evaluate the impact of laparoscopy in the surgical treatment for FIGO stage I ovarian cancer (stages Ia,Ib, Ic) when compared with laparotomy.
The following issues will be addressed in this review:
(1) Is laparoscopy (intervention group) effective in improving overall survival compared with laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(2) Is laparoscopy (intervention group) effective in reducing progression-free survival compared with laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(3) Does primary laparoscopy result in less surgical complications than laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(4) Does primary laparoscopy (intervention group) result in more local recurrence (port site) than laparotomy (control group) in midline incision in patients with FIGO Stage I ovarian cancer?
(5) Does primary laparoscopy (intervention group) result in more distant recurrence than laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(6) Does primary laparoscopy (intervention group) result more tumour spillage at the time of surgery than laparotomy (control group) in patients with FIGO Stage I ovarian cancer?

BACKGROUND

Malignant ovarian neoplasms are responsible for four per cent of all cancer affecting women and are the second most common cause of death from gynaecological cancer and the fourth most common cause of death from all types of cancer affecting women (Yancik 1993). Diagnosis of early ovarian cancer (limited to the ovaries) is rare and is mainly made by accidental discovery at the time of routine sonography or during laparoscopy. The incidence of managing an unexpected ovarian cancer by laparoscopy is 6.5 in 1000 women with an adnexal mass (Wenzl 1996).

Most cancers of the ovary are epithelial types. The most common subtype are serous tumours, which comprise from 40% to 70% of all types; endometrioid tumours are the second most common, approximately 20% to 25% of all cases. Mucinous epithelial tumours are rarer, comprising 5% to 20% of cases (Kosary 1994). Borderline ovarian tumours constitute approximately 5.9% of primary epithelial ovarian cancers (Medeiros 2005). However, the diagnosis of borderline ovarian tumours is more difficult because histopathologic criteria used for differential diagnosis between borderline and malignant lesions vary in different countries (Burger 2000). Stromal and germ cell tumours make up 1.1% to 1.7% of all cases of malignant ovarian tumours (Medeiros 2005).

The prognosis of all ovarian tumours are independently affected

by the following: stage of cancer at diagnosis, histological subtype and grading and the volume of residual disease (Benedet 2000). Current standard treatment for patients with early stage ovarian cancer is a laparotomy with a longitudinal median incision to permit the necessary surgical staging that is required (Benedet 2000; Hand 1993; Kosary 1994). The primary tumour, if limited to the ovary, must be examined to look for capsular rupture (Benedet 2000). There is evidence that overall survival rate could be high when the transformed cells are confined within the ovaries (Crayford 2000). Conservative therapy can be proposed in patients who desire to remain fertile in borderline tumours with an obviously limited disease (stage Ia) and normal examination of the opposite ovary (Benedet 2000; Vinatier 1996). For all patients, the proposed surgical treatment includes total hysterectomy and bilateral salpingo-oophorectomy and all obvious sites of tumour must be removed (Benedet 2000; Vinatier 1996). Further, the omentum, pelvic and para-aortic lymph nodes should be removed for histological examination to adhere to these oncological principles for accurate staging procedures in early disease (Benedet 2000; Vinatier 1996).

Recently two parallel randomised clinical trials (RCTs)- International Collaborative Ovarian Neoplasm 1 (ICON1) and Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) in early-stage ovarian cancer that compared platinum-based adjuvant chemotherapy with observation following surgery found that adjuvant chemotherapy would provide further benefits for women with stage I ovarian cancer (Trimbo 2003). ICON1 reported an improvement of overall survival of 8% and recurrence-free survival of 11% in patients treated with adjuvant platin-based chemotherapy compared with observation (Trimbo 2003). However, ACTION also showed that adjuvant chemotherapy only improved the overall and disease-free survival significantly in inadequately staged patients (Trimbo 2004), though this was a post hoc sub group analysis. In addition, a systematic review led by Elit et al. found similar results, especially when patients did not receive lymphadenectomy as part of the surgical staging (Elit 2004). Therefore in the patients who had undergone optimal surgical staging, adjuvant chemotherapy may have had no effect on the prognosis (Trimbo 2004; Vergote 2003). Many believe that the best policy for the treatment of patients with early ovarian cancer is to make every effort to achieve optimal surgical staging and to reserve adjuvant chemotherapy for those patients in whom optimal staging is not feasible (Trimbo 2004). There have, however, been no randomised trials addressing optimal staging or surgery.

Laparoscopy has been considered the surgical procedure that should be restricted to patients with pre-operative evidence that the cyst is benign (Vergote 2004). The inappropriate treatment of a malignant condition by endoscopy is associated with an impaired prognosis (Lehner 1998). Rupture of an ovarian malignant tumour should be avoided at the time of surgery for an early ovarian cancer (Vergote 2004). Some endoscopic procedures are performed using CO2 laser techniques, and this is considered by some authors to increase the risk of activating cell enzymes which may lead to mitosis and an increase in the production of tumour growth factor. If the duration of the surgery is prolonged there may also be excess mechanical or chemical damage of the mesothelium which, in some cases of malignancy being inadvertently treated as a benign lesion, may increase the risks of metastases in the abdominal cavity (Greene 1995; Volz 1999). However, reports addressing the selective use of laparoscopic techniques in the management of malignant gynaecologic disease have been published with increasing frequency (Chi 1999; Dottino 1999; Kadar 1997; Vinatier 1996), but it remains controversial whether laparoscopy is a good choice for early ovarian cancer (Vergote 2004).

It is not yet established whether laparoscopy is as good as or better than the conventional surgical approach for treatment for ovarian tumours which are assumed to be malignant. Given the limited evidence from randomised trials in this area of surgery, and the concerns which have been expressed over quality, an objective analysis of the literature evidence requires evaluation of both randomised and non-randomised studies. We intend to perform a systematic review to compare laparoscopy and laparotomy as a surgical approach for the treatment of early stage ovarian cancer. The conclusions of this study could help implement management protocols validated by good levels of evidence, and highlight where there is a need for further research.

OBJECTIVES

The objective of this review will be to evaluate the impact of laparoscopy in the surgical treatment for FIGO stage I ovarian cancer (stages Ia,Ib, Ic) when compared with laparotomy.

The following issues will be addressed in this review:
(1) Is laparoscopy (intervention group) effective in improving overall survival compared with laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(2) Is laparoscopy (intervention group) effective in reducing progression-free survival compared with laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(3) Does primary laparoscopy result in less surgical complications than laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(4) Does primary laparoscopy (intervention group) result in more local recurrence (port site) than laparotomy (control group) in midline incision in patients with FIGO Stage I ovarian cancer?
(5) Does primary laparoscopy (intervention group) result in more distant recurrence than laparotomy (control group) in patients with FIGO Stage I ovarian cancer?
(6) Does primary laparoscopy (intervention group) result more tumour spillage at the time of surgery than laparotomy (control group) in patients with FIGO Stage I ovarian cancer?

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Inclusion criteria

Studies regarding patients with histologically proven stage I ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) will be included in this review.

Studies comparing laparoscopic surgery with laparotomy for early ovarian cancer are only available from 1990.

It is anticipated that a very small number of randomised controlled trials (RCTs) have been conducted on early stage ovarian cancer. Therefore, non-randomised comparative studies, cohort studies and case-controls studies, but not studies with historical controls, will also be considered for this review.

Histological sub grouping for malignant ovarian tumours will be considered whenever possible (Scully 1999):
(1) Surface epithelial-stromal tumours:
(a) serous type (borderline and malignant)
(b) mucinous type (borderline and malignant)
(c) endometrial tumours

(2) Germ cell tumours:
(a) teratoma (immature and monodermal types)
(b) dysgerminoma
(c) yolk sac tumour
(d) embryonal carcinoma
(e) carcinoid tumours

(3) Sex cord-stromal tumours:
(a) granulosa-stromal cell tumours
(b) sertoli-stromal cell tumours (androblastoma)
(c) sex cord tumour with annular tubules
(d) gynandroblastoma
(e) unclassified sex cord-stromal tumour
(f) steroid (lipid) cell tumour

Exclusion criteria

All studies regarding patients with early stage ovarian cancer who desired to remain fertile, treated by conservative surgery (unilateral salpingo-oophorectomy).
All studies where the stage of ovarian cancer was inadequately staged.

Types of participants

Patients with early stage ovarian cancer will be included, i.e. patients with disease confined to the ovaries, no lymph node involvement or distant metastases.
The International Federation of Gynecology and Obstetrics (FIGO) distinguishes patients with stage I ovarian cancer as follows (Scully 1999):
Stage Ia: unilateral tumours
Stage Ib: bilateral tumours
Stage Ic: identifies tumour spillage, tumour capsular penetration, positive peritoneal cytology
No lymph node involvement or distant metastases

Whenever possible the results will be stratified by:
Histological subgroups of ovarian cancer

Types of intervention

In this review two surgical approaches used for the management for FIGO Stage I ovarian cancer will be compared: laparoscopy (intervention group) and laparotomy (control group).

Types of outcome measures

Primary outcomes

(1) Survival at five years.
(2) Progression-free survival at five years.

Secondary outcomes

(1) Tumour spillage at time of surgery.
(2) Local recurrence: laparoscopy (porte site) and laparotomy (midline incision).
(3) Distant recurrence.
(4) Surgical outcome:

(a) Surgical complications (immediate and delayed):
(i) injury (bladder, urether, vascular, small bowel and colon injuries);
(ii) presence/complication of adhesions;
(iii) febrile morbidity;
(iv) intestinal obstruction;
(v haematoma;
(vi) infection;
(vii) conversion to laparotomy rate.

(b) Systemic complications:
(i) chest infection;
(ii) deep venous thrombosis;
(iii) pulmonary embolism;
(iv) cardiac failure;
(v) cardiac ischemias;
(vi) cerebrovascular accident

(c) Operative time.
(d) Recovery from surgery: length of hospital day and re-admission rates.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Gynaecological Cancer Group methods used in reviews.

Searches will be conducted to identify all published and unpublished RCTs and non RCTs comparing laparoscopy and laparotomy for early stage ovarian cancer. The search strategy will

identify studies in all languages and, when necessary, non English language papers will be translated so that they could be fully assessed for potential inclusion in the review.

Trials will be identified by searching the Cochrane Gynaecological Cancer Group trials register, Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3, 2004), MEDLINE (January 1990 to date), EMBASE (1990 to date), LILACS (1990 to date), BIOLOGICAL ABSTRACTS (1990 to date) and Cancerlit (1990 to date).

MEDLINE will be searched using the following keywords:
1. Randomized controlled trial. pt.
2. Controlled clinical trial.pt
3. Randomizes controlled trials/
4. random allocation/
5. double -blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt
9. exp clinical trials/
10. (clin$ adj25 trial$).ti,ab,sh.
11. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or masks$)).ti,ab,sh.
12. placebos/
13. placebo$.ti,ab,sh
14. random$.ti,ab,sh.
15. Research design/
16. or/8-15
17. (animal not human).sh
18. 16 not 17
19. comparative study.sh
20. exp evaluation studies
21. follow up studies.sh
22. prospective studies
23. (control$ or prospectiv$).mp or volunter$.ti.ab.
24. exp cohort studies/
25. cohort.tw
26. exp longitudinal studies/
27. (cohort adj5 (stud$ or trial$)).tw
28. (prospectiv$ adj5 (stud$ or trial$)).tw
29. (longitudinal adj5 (stud$ or trials)).tw
30. or/18-29
31. exp Ovarian Neoplasms/
32. (ovar$ adj5 tumo?r).tw
33. (ovar$ adj5 neoplas$).tw
34. (ovar$ adj5 cancer$).tw
35. (ovar$ adj5 carcino$).tw
36. exp Adnexal Diseases/
37. exp Ovarian Cancer/
38. or/31-37
39. exp “early ovarian cancer”/
40. exp “early ovarian neoplasm”/
41. “stage I ovarian cancer”/
42. or/ 39-41
43. 38 and 42
44. exp SURGERY/
45. surg$.tw.
46. laparo$.tw.
47. exp Surgical procedures, Operative/
48. or/44-47
49. 43 and 48
50. 30 and 49

EMBASE will be searched using the following keywords:
1. Controlled study/or Randomized Controlled trial/
2. double blind procedure/
3. single blind procedure/
4. crossover procedure/
5. drug comparison/
6. placebo/
7. random$.ti,ab,hw,tn,mf.
8. latin square.ti,ab,hw,tn,mf.
9. crossover.ti,ab,hw,tn,mf.
10. cross-over.ti,ab,hw,tn,mf.
11. placebo$.ti,ab,hw,tn,mf.
12. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
13. (comparative adj5 trial$).ti,ab,hw,tn,mf.
14. (clinical adj5 trial$).ti,ab,hw,tn,mf.
15. or/ 1-14
16. nonhuman/
17. (animal not human)/
18. or/16-17
19. 15 not 18
20. comparative study.ti,ab,hw,tn,mf.
21. follow up studies.ti,ab,hw,tn,mf.
22. prospective studies.ti,ab,hw,tn,mf.
23. (control$ or prospectiv$).mp or volunteer$.ti.ab.
24. cohort studies/
25. cohort.ti,ab,hw,tn,mf.
26. longitudinal studies.ti,ab,hw,tn,mf.
27. (cohort adj5 trial$).ti,ab,hw,tn,mf.
28. (prospectiv$ adj5 trial$).ab,hw,tn,mf.
29. (longitudinal adj5 trials).ti,ab,hw,tn,mf.
30. or/19-29
31. exp Ovarian Neoplasms/
32. (ovar$ adj5 tumo?r).tw
33. (ovar$ adj5 neoplas$).tw
34. (ovar$ adj5 cancer$).tw
35. (ovar$ adj5 carcino$).tw
36. exp Adnexal Diseases/
37. exp Ovarian Cancer/
38. or/ 31-37
39. exp “early ovarian cancer”/
40. exp “early ovarian neoplasm”/
41. “stage I ovarian cancer”/

42. or/39-41
43. 38 and 42
44. exp SURGERY/
45. surg$.tw.
46. laparo$.tw.
47. exp Surgical Technique
48. or/43-46
49. 43 and 48
50. 30 and 49

CENTRAL on the current issue of The Cochrane Library, the National Research Register (NRR) and Clinical Trials register will also be searched in all fields using the following words: ovarian cancer, laparotomy, laparoscopy, ovarian surgery.

The citation list of relevant publications, abstracts of scientific meetings and list of included studies will also be checked through hand searching and experts in the field contacted to identify further reports trials. The results of handsearching of the following conferences will be searched:

Gynecologic Oncology
International Journal of Gynecological Cancer
British Journal of Cancer
British Cancer Research Meeting
Annual Meeting of the International Gynecologic Cancer Society
Annual Meeting of the American Society of Gynecologic Oncologist
Annual Meeting of The European Society of Medical Oncology (ESMO)
Annual Meeting of the American Society of Clinical Oncology (ASCO)

METHODS OF THE REVIEW

Selection of studies
All eligible studies will be assessed for their methodological quality and relevance to the review objectives. Study selection will be undertaken by reviewers. No effort will be made to blind the reviewers for names of authors, institutions and journals. The reason for this is that all reviewers are too familiar with the literature on early stage ovarian cancer treatment. As it is known to us that only a small number of RCTs have been published, we will also incorporate other types of studies in this review, i.e. cohort studies and case-control studies, but not studies with historical controls.

The quality of allocation concealment for RCTs will be graded as either adequate (A), unclear (B), or inadequate (C) , following the detailed descriptions of these categories provided by the Cochrane Gynaecological Cancer Group.

All studies will be assessed with the aid of a critical review form. We will use three different critical review forms: one for RCTs, one for case control studies and one for cohort studies (Table 01; Table 02; Table 03). The critical review forms will be filled out independently by the reviewers to assess whether the studies meet the inclusion criteria. Data to be extracted will include trial characteristics, characteristics of the study participants, interventions and outcomes (see additional tables Table 04; Table 05; Table 06; Table 07).

Differences will be resolved by discussion. Further information will to be sought from the authors/principal investigators where papers contain insufficient information to make a decision about eligibility or where additional information is required.

Statistical Analysis
Statistical analysis will be performed in accordance with the guidelines developed by the Cochrane Gynaecological Cancer Group. All trials will initially be included in one analysis of surgical laparoscopy and laparotomy for early stage ovarian cancer. Statistical heterogeneity between the results of different studies will be examined by checking the usual test statistic (Cochran's *Q*) where P values are obtained by comparing the statistic with a chi-square distribution. Care must be taken in the interpretation of the chi-squared test, since it has low power in the (common) situation of a meta-analysis when trials have small sample size or are few in number. If there is no evidence of statistical heterogeneity ($p > 0.10$), a fixed effects model will be used. If there is significant heterogeneity ($p < 0.10$), the possible clinical and methodological reasons for this will be explored qualitatively and a random effects model will be used (Deeks 2003). However, since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable. Alternative approach that quantifies the effect of heterogeneity is inconsistency (I^2), providing a measure of the degree of inconsistence in the studies' results with 95% uncertainty intervals (Higgins 2003). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value of 0% indicates no observed heterogeneity and a value greater than 50% may be considered substantial heterogeneity. If it is inappropriate to pool the data because of clinical or statistic heterogeneity a systematic review without meta-analysis will be performed or a meta-analysis excluding outlying studies will be performed.

If sufficient trials of adequate quality are available and their populations are clinically similar, meta-analyses of primary and secondary end-points will be carried out. For meta-analyses of the time-to-event outcomes, the most appropriate statistic is the hazard ratio (HR) and where this is provided in a trial report, it will be used. Where it has not been provided, it will be estimated indirectly from other summary statistics if possible (Parmar 1998). Where this is not possible, the odds ratio will be calculated and interpreted with caution, bearing in mind the possibility of mortality/morbidity and hence the odds ratio, being influenced by length of follow-up.

For meta-analyses of dichotomous outcomes, relative risks (RR) will be calculated with 95% confidence intervals (CIs) and

combined for meta-analysis with RevMan software .

Continuous data will be combined for meta-analysis. We will use mean and standard deviations to derive a weighted mean difference (WMD) with 95% CIs using a fixed effect model. As a general rule, a fixed effect model will be used for calculations of summary estimates and their 95% CIs unless there is significant heterogeneity in which case results will be confirmed using a random effects statistical model.

Where possible, subgroup analyses will be planned to compare the study results for kinds of intervention, histological types, study design and reporting (adequate versus unclear allocation concealment for RCTs).

POTENTIAL CONFLICT OF INTEREST

None

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

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ADDITIONAL TABLES

Table 01. Critical review form: randomized studies

No.	Question	Yes/No
1.	Was the assigned treatment adequately concealed prior to allocation?	
2.	Were the outcomes of patients who withdrew or were excluded after allocation described and included in an "intention to treat" analysis?	
3.	Were the withdrawals < 15% of the study population?	
4.	Were the inclusion and exclusion criteria for entry clearly defined?	
5.	Were the treatment and control group comparable at entry?	
6.	Were the subjects blind to assignment status following allocation (if trial design allowed it)?	
7.	Were the care programmes, other than the trial options, identical?	
8.	Were there any checks to ensure compliance to treatment?	
9.	Were the outcome assessors blind to assignment status?	
10.	Were the outcome measures used clearly defined?	
11.	Were the accuracy, precision, and observer variation of the outcome measure adequate?	

12. Was the timing of the outcome measure appropriate?

13. Were the outcome measures clearly reported?

Table 02. Critical review form: case control studies

No.	Question	Yes/No
1.	Did study population meet our criteria?	
2.	Is it possible to analyse patients that meet our criteria separately?	
3.	Were patients analysed in the groups to which they were assigned?	
4.	Were the groups similar before treatment?	
5.	Aside from the experimental intervention, were the groups treated equally?	
6.	Were all patients accounted for at the end of follow up?	
7.	How long was follow up?	
8.	Were interventions defined adequately?	

Table 03. Critical review: cohort studies

No.	Question	Yes/No
1.	Did study population meet our criteria?	
2.	Is it possible to analyse patients that meet our criteria sepatately?	
3.	Were all observed patients accounted for at the end of follow up?	
4.	How long was follow up?	
5.	Were interventions defined adequately?	
6.	How precise was the estimate of the treatment? -disease free survival - complications	
7.	Were all clinically important outcomes considered? - disease free survival - complications	

Table 04. Data extraction: trial characteristics

No.	Question	Answer
1.	Method of randomization, in order of preference, as follows: (a) third party randomization (pharmacy, computer or telephone) (b) true randomization (opaque numbered envelope or register)	
2.	Study design (a) duration of follow-up (2) type of follow-up (3) presence or absence of blinding to allocation	

Table 04. Data extraction: trial characteristics (*Continued*)

No.	Question	Answer
3.	Size of study (a) number of women recruited (b) number of women randomized/ case control and cohort (c) number of women excluded (d) number of women withdrawn and lost to follow-up (e) number of women analysed	
4.	Study setting (a) single-centre or multicentre (b) location (c) timing and duration	
5.	Analysis (a) whether a power calculation was performed and adhered to (b) whether 'intention to treat' analysis was performed by authors	
6.	Criteria for ovarian surgery (a) indications specified (b) data broken down by indications surgery	

Table 05. Data extraction: characteristics of the study participants

No	Question	Answer
1.	Baseline characteristics (a) age (b) stage of early ovarian cancer by FIGO (c) methods used to define and diagnose participants (d) previous treatments and surgery (e) how were participants found (f) reasons for exclusion of participants	
2.	Treatment characteristics (a) pre-operative preparation (b) level of training of surgeons	

Table 06. Data extraction: intervention

No	Question	Answer
1.	All randomised controlled trials (RCTs) comparing laparoscopy with laparotomy in women with an ovarian tumour assumed to be malignant. Where possible are considering the results will be stratified by type of oncologic surgeon: gynaecologists and/or surgeon.	
2.	Laparoscopy for multiple cytologic washings, bilateral salpingo-oophorectomy, hysterectomy, omentectomy, random peritoneal biopsies and retroperitoneal lymph node sampling	
3.	Laparotomy for multiple cytologic washings, bilateral salpingo-oophorectomy, hysterectomy, omentectomy, random peritoneal biopsies and retroperitoneal lymph node sampling	
4.	Strategies to reduce the likelihood of complications	
5.	Absence of co-interventions in treatment and control groups	

Table 07. Data extraction: outcomes

No.	Question	Answer
1.	Mortality at 5 years	
2.	Recurrence of disease - at 5 years	
3.	Morbity - post- surgical complications (surgical injury: bladder, urether, vascular, small bowel and colon injuries; presence/complication of adhesions; febrile morbidity, intestinal obstruction; infection incision umbilical; infection incision abdominal; urinary tract infection; urinary retention; chemical peritonitis; intestinal obstruction; thromboembolism) immediate and delayed	
4.	Survival at 5 years	
5.	The number of harvested lymph nodes in laparoscopy and laparotony	
6.	Rate of convertion to laparotomy	
7.	Quality of life at 1 year	
8.	Operatin time	
9.	Recovery (length of hospital day and re-admission rates)	

COVER SHEET

Title	Laparoscopy versus laparotomy for FIGO Stage I ovarian cancer
Authors	Medeiros LR, Rosa DD, Bozzetti MC, Edelweiss MI, Stein AT, Pohlmann P, Zelmanowicz A, Ethur AB, Zanini RR
Contribution of author(s)	Lidia Medeiros: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods, search strategy. Daniela Dorneles Rosa: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods, search strategy. Anaelena Ethur: Took the lead in writing the protocol and statistical analysis. Roselaine Zanini: Took the lead in writing the protocol and statistical analysis. Mary Clarisse Bozzetti: Took the lead in writing the protocol, developed background and initial objectives. Airton Stein: Contributed to background section, selection criteria, initial objectives, methods and search strategy. Maria Isabel Edelweiss: developed background and initial objectives. Alice Zelmanowicz: Took the lead in writing the protocol, developed background, initial objectives, selection criteria, methods, search strategy. Paula Pohlmann: Took the lead in writing the protocol, developed background, initial objectives, selection criteria.
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