Published in final edited form as:

Am J Obstet Gynecol. 2017 January ; 216(1): 50.e1–50.e12. doi:10.1016/j.ajog.2016.08.030.

Laparoscopic Staging for Apparent Stage I Epithelial Ovarian Cancer: Analysis of the National Cancer Data Base

Alexander Melamed, MD, MPH¹, Nancy L. Keating, MD, MPH², Joel T. Clemmer, MA¹, Amy J. Bregar, MD, MS¹, Jason D. Wright, MD³, David M. Boruta, MD¹, John O. Schorge, MD¹, Marcela G. Del Carmen, MD, MPH¹, and J. Alejandro Rauh-Hain, MD¹

¹Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

²Department of Health Care Policy, Harvard Medical School, and Division of General Internal Medicine, Brigham and Women's Hospital, Boston, MA

³Departments of Obstetrics and Gynecology and Herbert Irving Comprehensive Cancer Center, Columbia University, and New York Presbyterian Hospital, New York, NY

Abstract

Background—While advances in minimally invasive surgery have made laparoscopic staging technically feasible in stage I epithelial ovarian cancer, the practice remains controversial due to an absence of randomized trials and lack of high-quality observational studies demonstrating equivalent outcomes.

Objective—This study seeks to evaluate the association of laparoscopic staging with survival among women with clinical stage I epithelial ovarian cancer.

Study Design—We used the National Cancer Data Base to identify all women who underwent surgical staging for clinical stage I epithelial ovarian cancer diagnosed from 2010-2012. The exposure of interest was planned surgical approach (laparoscopy versus laparotomy) and the primary outcome was overall survival. The primary analysis was based on intention-to-treat: all women whose procedures were initiated laparoscopically were categorized as having had a planned laparoscopic procedure regardless of subsequent conversion to laparotomy. We used propensity methods to match patients who underwent planned laparoscopic staging with similar patients who underwent planned laparotomy based on observed characteristics. We compared survival among the matched cohorts using the Kaplan-Meier method and Cox regression. We compared extent of lymphadenectomy using the Wilcoxon rank-sum test.

Corresponding Author: J. Alejandro Rauh-Hain, MD, Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, 55 Fruit Street, Yawkey 9 E Boston, Massachusetts 02114, Phone: (617) 726-1940, Fax: (617) 724-6898, jrauh-hain@partners.org.

Disclosure of Interests: The authors declare that there are no conflicts of interest.

This study was presented as a poster at the 2016 Society of Gynecologic Oncology Annual Meeting, San Diego, California.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—Among 4,798 eligible patients, 1,112 (23.2%) underwent procedures which were initiated laparoscopically, of which 190 (17%) were converted to laparotomy. Women who underwent planned laparoscopy were more frequently white, privately insured, from wealthier zip codes, received care in community cancer centers, and had smaller tumors that were more frequently of serous, and less often of mucinous histology than those who underwent staging via planned laparotomy. After propensity score matching, time to death did not differ between patients undergoing planned laparoscopic versus open staging (Hazard Ratio=0.77, 95% CI=0.54-1.09; $p=0.13$). Planned laparoscopic staging was associated with a slightly higher median lymph node count (14 versus 12, $p=0.005$). Planned laparoscopic staging was not associated with time to death after adjustment for receipt of adjuvant chemotherapy, histological type and grade, and pathologic stage (Hazard Ratio 0.82, 95% CI 0.57-1.16).

Conclusion—Surgical staging via planned laparoscopy versus laparotomy was not associated with worse survival in women with apparent stage I epithelial ovarian cancer.

Keywords

laparoscopy; laparotomy; ovarian cancer; staging

Introduction

Ovarian cancer is the 5th leading cause of cancer-associated death among women.(1) Although most patients with epithelial ovarian cancer present with advanced-stage disease, patients with early-stage ovarian cancer have a good prognosis; the 5-year survival for patients with surgically-evaluated stage I disease is approximately 90%.(2) Patients with ovarian cancer that appears confined to the ovary require surgical staging, a procedure traditionally performed via exploratory laparotomy, which includes salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, omentectomy, peritoneal washings, and peritoneal biopsies.(3) Hysterectomy and removal of apparently uninvolved adnexa are also recommended for patients not seeking future fertility.

Laparoscopic surgery has been proposed as an alternative to laparotomy for surgical staging and the treatment of apparently early stage ovarian cancer.(4) Compared with laparotomy, minimally-invasive surgery is associated with fewer complications and a shorter recovery period, and has been adopted in early stage endometrial cancer.(5) While advances in minimally invasive surgery have made laparoscopic staging technically feasible in stage I epithelial ovarian cancer, the practice remains controversial due to an absence of randomized trials, and lack of high-quality observational studies demonstrating equivalent outcomes. Most published studies are small, many lack comparison groups, while others do not control for possible confounding.(6-12) A recent systematic review for Cochrane Library concluded that paucity of high quality evidence precluded assessment of the safety of laparoscopic staging in stage I ovarian cancer.(13) The present study uses a national tumor registry database to compare outcomes between women who underwent laparoscopic staging and those who underwent staging via laparotomy for apparent stage I epithelial ovarian cancer.

Materials and Methods

We used data from the National Cancer Data Base, a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, which aggregates tumor registry data from over 1,500 hospitals, and includes 70% of all incident cancer diagnosis in the United States.(14) The National Cancer Data Base includes information about patient demographics, tumor characteristics, cancer-directed therapies (surgery, radiation, and chemotherapy), treating facility, and overall survival. This investigation was exempt from Institutional Review Board oversight.

The study cohort flow diagram is illustrated in Figure 1. We identified all patients diagnosed with epithelial ovarian cancer from 2010 to 2012 in the 2013 National Cancer Data Base public use data file. We defined women who underwent surgery for apparent stage I ovarian cancer as those with American Joint Committee on Cancer 7th edition clinical stage I, IA, IB or IC. We also include patients with missing American Joint Committee on Cancer clinical stage who were American Joint Committee on Cancer pathologic stage I, IA, IB or IC.(15) We excluded women with cancer diagnoses that were not microscopically confirmed, and those with histologic codes that did not correspond to serous, mucinous, clear cell, endometrioid, or other adenocarcinoma of the ovary (Appendix Table 1).(16) Because the National Cancer Data Base suppresses facility type for women younger than 40 years, precluding adjustment for this variable, these women were excluded. We also excluded women who did not undergo lymphadenectomy, had surgery more than 80 days after diagnosis, had missing data on surgical approach, received chemotherapy or radiation prior to surgery, or had a cancer diagnosis in addition to ovarian cancer.

The exposure of interest was planned surgical approach. In the primary analysis, we considered all subjects whose staging procedure was initiated with a minimally invasive approach (laparoscopy or robot-assisted laparoscopy) as having undergone a planned laparoscopic staging procedure, irrespective of whether the procedure was completed laparoscopically or via laparotomy.

The primary outcome was overall survival defined as months from cancer diagnosis to death, or the date of last contact as recorded by the cancer registry. Secondary outcomes included cumulative survival at three and four years after diagnosis, and frequency of death within 90 days of surgery. We also compared frequency of unplanned readmission within 30 days of surgical discharge, length of stay after surgery, and pathologic lymph node count.

Control variables included patient age at the time of diagnosis (categorized as 40-49, 50-59, 60-69, 70-79 and 80 years or older), race-ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black or Other), tumor histology (Appendix Table 1), and tumor grade. Receipt of any adjuvant chemotherapy was categorized as yes, no, or unknown. We grouped tumors as smaller than 1 cm, 1.0-4.9 cm, 5.0-9.9cm, and 10 cm or larger in tables, and by 1 cm increments for calculation of propensity scores. Extent of comorbidity was categorized as zero, one, or more than one comorbidities, using the Deyo adaptation of the Charlson comorbidity index.(17-18) Location of treating facility was categorized by United States Census Region (Northeast, South, Midwest, and West).(19) We identified rural residence

based on zip code when the United State Department of Agriculture classified the county as “completely rural or less than 2,500 urban population, not adjacent to a metro area.”(20) The median household income, as estimated by the 2012 American Community Survey, in the subject's zip code of residence was used as a proxy for subjects' income, and categorized according to quartiles across all United States zip codes. Insurance status was categorized as uninsured, privately insured, insured by Medicare, or having another type of government insurance (military or Medicaid). The treating facility was categorized according to the Commission on Cancer accreditation program as a community cancer program, comprehensive community cancer program, academic/research program, integrated network cancer program, or other.

Analyses

We compared the frequency of 30-day readmission, death within 90 days of surgery, lymph node count, and post-operative length of stay using the Wilcoxon rank-sum and χ^2 tests. We employed propensity score matching to create a cohort in which subjects who underwent planned laparoscopy and laparotomy were balanced on measured covariates that might confound the effect of planned surgical approach on overall survival.(21) We estimated the propensity to undergo planned laparoscopic staging with a logistic regression model with variables selected *a priori* based on their potential to influence the likelihood of a subject undergoing laparoscopic surgery. The independent variables included age, race-ethnicity, tumor size, treating facility type, insurance status, income, number of comorbidities, census region, rural status, and year of diagnosis. We employed a 1:1 optimal matching algorithm with caliper set to 0.2 standard deviations of the logit of the propensity score to identify matches.(22, 23) We evaluated the success of propensity score matching using absolute standardized differences, with dummy variables used in the case of nominal/ordinal covariates, considering covariates well balanced when the absolute standardized difference was less than 10% (Appendix Figure 1).(24)

We plotted survival functions for women who underwent planned laparoscopic staging and those who underwent planned staging laparotomy in the propensity score matched cohort using the Kaplan Meier method, and compared these using the log rank test. We estimated the hazard ratio for overall mortality after planned laparoscopic staging using a Cox proportional hazard model. We also estimated survival rates, and associated 95% confidence intervals, at three, and four years after diagnosis, and compared these with the Z-test for independent proportions. To adjust for potential confounding introduced by factors that may have been evident only after surgical staging, we also calculated the hazard ratio for overall mortality after planned laparoscopic staging using a Cox proportional hazard model that included pathological stage, receipt of adjuvant chemotherapy, tumor grade, and histologic type as covariates.

Sensitivity Analyses

To evaluate whether the effect of planned laparoscopy was sensitive to receipt of adjuvant chemotherapy, we stratified the propensity-matched cohort by chemotherapy status and repeated the primary survival analysis in each group. To confirm that our findings persisted among patients whose procedures were planned and completed laparoscopically we repeated

all analyses after excluding women whose procedures were initiated laparoscopically but completed by laparotomy. Because propensity-score matching and Cox regression control only for observed characteristics, we investigated the robustness of the estimated treatment effect to the presence of potential unmeasured confounders.(25) We considered the possibility that two unobserved confounders, elevated serum CA-125, and suboptimal surgical staging, were associated with both the planned surgical approach and inferior survival. We calculated the hazard ratio (with associated 95% CI) for death after planned laparoscopic staging (relative to laparotomy) after adjustment for the presence of each potential confounder. Using published data, we estimated that preoperative CA-125 level of 30 U/mL was associated with an increased risk of death (Hazard Ratio=1.65), and that undergoing suboptimal staging was associated increased risk of death (Hazard Ratio=2.31) among patients who did not receive chemotherapy, but had no effect among those who did. (25-27). We considered a range of scenarios, with the assumptions that elevated CA-125 was more prevalent among patients who underwent laparotomy, and that suboptimal staging was more prevalent among subjects who underwent laparoscopy (see appendix for details).

All statistical analysis was performed using R 3.0.3 (*R Foundation for Statistical Computing, Vienna Austria*).

Results

Of the 4,798 patients who met study criteria, 1,112 (23.2%) underwent planned laparoscopic surgery for clinical stage I epithelial ovarian cancer (Figure 1). Of these, 190 (17.1%) had conversion to laparotomy. Among the 922 patients whose staging surgery was completed laparoscopically, 367 (39.4%) underwent robotic-assisted laparoscopy. Patients who underwent planned laparoscopic surgery were more likely to be white, receive treatment in non-academic facilities, live in higher income areas, reside in the Northeast or South, have private insurance, and have fewer comorbidities than patients who underwent laparotomy (Table 1). Laparoscopically staged patients had smaller tumors that were more frequently serous, and less frequently mucinous, than women who underwent open surgery (Table 1).

We matched 1,096 subjects (98.6%) who underwent planned laparoscopic staging to subjects who had staging by laparotomy. Associations between demographic, socioeconomic and histopathologic covariates and receipt of laparoscopic surgery, seen in the total cohort, were not evident after propensity score matching (Table 1), suggesting that the matched cohort was well balanced on observed covariates. Balance of covariates was confirmed with absolute standardized differences, which were less than 10% for all variables after propensity score matching (Appendix Figure 1).(14)

The frequency of surgical complications as measured by death within 90-days of surgery (0.3% versus 0.9%; $p=0.10$) and unplanned readmission within 30 days of surgical discharge (2.8% versus 3.9%; $p=0.37$) did not differ between subjects who had planned laparoscopy and propensity-matched patients who had planned laparotomy (Table 2). However, subjects who underwent planned laparoscopic surgery had higher lymph node counts (median: 14 versus 12 nodes; $p=0.005$) and shorter postoperative hospital stays (median: 3 versus 4 days; $p<0.001$). Women who underwent staging by laparotomy were more likely to be upstaged on

final pathologic examination. In subjects with known clinical stage, 81 of 665 (12.2%) who underwent planned laparoscopy and 126 of 656 (19.2%) who had planned laparotomy were upstaged on final pathological evaluation ($p < 0.001$); 27 and 51 women in each respective group had positive lymph nodes (4.0% versus 7.8%, $p = 0.005$).

After propensity score matching, the median duration of follow up after diagnosis was 29.9 month. There were 55 and 71 deaths in the laparoscopy and laparotomy groups, respectively. We found no significant difference in overall survival between women who underwent planned laparoscopic staging and those who had a planned staging laparotomy (Figure 2, rank sum $p = 0.13$) and time to death did not differ significantly for women who underwent staging by planned laparoscopy versus laparotomy (Hazard Ratio=0.77, 95%CI=0.54-1.09). Additionally, we found no differences in three- and four-year survival rates by group (Table 2). Planned laparoscopic staging was not associated with risk of death after adjustment for receipt of adjuvant chemotherapy, histological type and grade, and pathologic stage (Hazard Ratio 0.82, 95%CI=0.57-1.16).

Sensitivity analyses

After stratifying the study population by receipt of adjuvant chemotherapy, we found no difference in survival between patients who underwent staging by laparoscopy and laparotomy irrespective of chemotherapy administration (not shown). In a secondary “as treated” analysis, in which we excluded patients who underwent conversion from laparoscopy to laparotomy from the laparoscopic group, we found no significant difference in overall survival between patients who underwent staging by laparoscopy and laparotomy (Hazard Ratio 0.80, 95%CI=0.54-1.19).

In analyses assessing sensitivity of our findings to unmeasured confounders, we found that within the range of plausible assumptions, differences in elevated preoperative serum CA-125 and suboptimal staging did not alter our conclusions about the lack of association of laparoscopic staging with survival (see Appendix). Even if CA-125 was more frequently elevated in patients who underwent laparotomy (1% versus 66%), adjustment for this confounder still did not result in a significant survival decrement for patients who underwent laparoscopy (adjusted Hazard Ratio 1.16, 95%CI=0.81-1.65, Appendix Table 2). When suboptimal staging in patients who did not receive adjuvant chemotherapy was assumed to be much more frequent in the planned laparoscopy group, adjustment for this potential confounder suggested a survival advantage for planned laparoscopy (Appendix Table 3). For example, if the prevalence of women who did not receive chemotherapy and had suboptimal staging was 20% in the laparotomy group and 40% in the laparoscopy group, adjustment for this confounder suggested that planned laparoscopy was associated with superior survival than laparotomy (adjusted Hazard Ratio 0.68, 95%CI=0.74-0.96).

Comment—Minimally invasive surgery has become common in gynecologic practice. Laparoscopic staging in early stage endometrial cancer is associated with shorter recovery time, shorter hospital stay, and improved cosmetic result than staging with laparotomy. (28-29) Nonetheless, due to a paucity of randomized trial and well designed observational studies, there are concerns regarding the use of laparoscopy in comprehensive surgical

staging of early ovarian cancer.(6-12) We have utilized a large population-based cancer database to evaluate the effect of planned mode of surgery on overall survival among women with clinical stage I epithelial ovarian cancer. We observed no difference in survival between women who underwent planned laparoscopic staging and those who underwent staging by laparotomy. By matching on propensity to undergo planned laparoscopic staging, we were able to adjust for many variables that may confound the association between mode of surgery and survival. Additionally, further adjustment for receipt of adjuvant chemotherapy, as well as final pathologic stage, grade, and histology did not influence our findings.

Our findings are consistent with previously reported retrospective series that have not demonstrated survival differences among women that underwent laparoscopic staging compared to laparotomy.(6-11) Nezhat and colleagues described a series of 20 women with ovarian and fallopian tube cancer who underwent laparoscopic staging and observed an 100% survival rate with no evidence of disease after nearly 5 years of follow-up.(6) Tozzi and colleagues described 24 patients with stage IA or IB ovarian or fallopian tube cancer who underwent comprehensive laparoscopic staging over a 7-year period.(7) At a median follow-up time of 46.4 months, the progression-free survival rate was 91.6%, and the overall survival rate was 100%.(7) However, seven of the 24 patients were found to have borderline ovarian tumors, which may have skewed the follow-up data in favor of an improved survival. In a prospective study by Ghezzi and colleagues of 26 patients staged by laparoscopy, the authors reported only one recurrence resulting in the death of the patient 12 months after surgery.(8) These results are echoed by other case series that report no recurrence or death in patients staged by laparoscopy at an approximate follow-up time of 2 years.(9-11) Despite the limitation of these small studies, their findings suggest that minimally invasive surgical staging of apparent early stage epithelial ovarian cancer is safe and effective when performed by a surgeon with appropriate training.(4)

Lymph node status is an important predictor of disease recurrence and survival; therefore, some authors propose that increased numbers of harvested nodes could be a marker for better surgical treatment.(30) We found that patients who underwent laparoscopy had more lymph nodes excised than those who underwent laparotomy, suggesting that staging quality was not inferior. In a study addressing feasibility of completion of laparoscopic staging for women with incompletely staged ovarian, fallopian tube, primary peritoneal, and uterine cancers sponsored by the Gynecologic Oncology Group, Spirtos and colleagues compared 58 patients who underwent comprehensive minimally invasive surgical staging with 17 patients who underwent laparotomy for completion staging, finding no difference in the number of pelvic and para-aortic lymph nodes excised.(31)

Women from the Northeast and South underwent laparoscopic staging more frequently than those from the Midwest and West. Interestingly, patients who underwent treatment at academic centers were less likely to have laparoscopic staging than those who were treated in community settings, as were non-white women, women living in lower-income areas, and women without private insurance. These findings suggest that socioeconomic factors and race/ethnicity may influence access to laparoscopic surgery for early ovarian cancer as well as clinical factors.(32-33)

Our analysis benefits from a large study population and its ability to adjust for patient's demographic characteristics, socioeconomic status, comorbidities and adjuvant treatment. Furthermore, we found concordant results in both our primary intention -to-treat and secondary as-treated analyses. Nonetheless, there are several limitations that must be considered in interpreting the findings. Surgeons' decisions regarding the surgical approach are based, at least in part, on factors that are not measured in the data which may act as unmeasured confounders. To minimize the impact of selection bias and confounding, we employed a propensity score analyses; and we also tested the sensitivity of our findings to two potential unobserved confounders, elevated CA-125 and suboptimal staging, and our findings were robust to these analyses. In addition, because the National Cancer Data Base began including mode of surgery in 2010, the current study has a relatively short median follow up time, and it is possible that survival difference may emerge after further observation. Finally, this study is underpowered to detect small difference in survival. With 126 deaths, at a significance level of 0.05, this study had 80% power to detect an unadjusted absolute difference in 4-year survival of 5.2% (91.5% versus 86.3%) similar to the absolute difference we observed in our adjusted analysis. Smaller differences may be clinically important; moreover, with a larger study population, we may have observed a small, statistically significant benefit to planned laparoscopy versus laparotomy. Furthermore, the National Cancer Data Base does not include information regarding disease recurrence which precluded analysis of this important outcome.

The National Cancer Data Base offers a large, nationally applicable sample to examine oncology practice patterns and outcomes in the United States.⁽³⁴⁾ Because early stage epithelial ovarian cancer is rare, a randomized clinical trial to evaluate mode of surgery, as has been performed in endometrial cancer, poses a considerable logistical challenge. Well designed observational studies may well produce the highest quality evidence available to evaluate the safety of laparoscopic management of early stage ovarian cancer. The current study suggests that, in the short term, laparoscopic staging is a safe alternative to staging laparotomy in women with apparent stage I epithelial ovarian cancer.

Acknowledgments

Funding: This work was supported by R25CA092203 from the National Cancer Institute at the National Institutes of Health and The Deborah Kelly Center for Outcomes Research, Massachusetts General Hospital. Dr. Keating is also supported by K24CA181510 from the National Cancer Institute.

Appendix

Analysis of sensitivity to unmeasured confounders

We considered the presence of two potential unmeasured confounders: elevated CA-125, and suboptimal staging in women not receiving adjuvant chemotherapy. We relied on a multicenter observational study by Paramasivam et al. to estimate the effect of CA-125 (> 30 IU/mL) on risk of death (hazard ratio [HR] 1.65), and the ACTION trial to estimate the impact of suboptimal staging on survival in women who did not receive chemotherapy (HR 2.31). [1,2] Since laparotomy is the standard of care for advanced ovarian cancer, and elevated CA-125 is associated with advanced disease, we assumed that surgeons were more

likely to perform a staging by laparotomy in women with elevated CA-125. Therefore, in all sensitivity analyses we assumed that subjects who underwent laparoscopic staging had lower prevalence of elevated CA-125 than those who underwent laparotomy. Because some surgical procedures involved in optimal surgical staging are more technically challenging when undertaken laparoscopically, we assumed that suboptimal staging was more frequent among women in the laparoscopy group. Additionally, because approximately 55% of patients in each group underwent adjuvant chemotherapy, the proportion of subjects who did not receive chemotherapy and underwent suboptimal staging could not exceed 45%.

We updated the hazard ratio for laparoscopy after adjusting for potential confounders under a variety of scenarios using the formula

$$aHR_{lapro} = \frac{HR_{lapro}}{HR_c P_1 + (1 - P_1) / (HR_c P_0 + (1 - P_0))}$$

described by Lin et al, where aHR_{lapro} is the hazard ratio after adjusting for an unmeasured confounder, HR_{lapro} is the hazard ratio for laparoscopy obtained from the Cox model in our main analysis, HR_c is the hazard ratio for death associated the unmeasured confounder, and P_0 and P_1 are the prevalence of the unmeasured confounder in the laparotomy and laparoscopy groups, respectively. [3]

Appendix Table 2 tabulates adjusted hazard ratios and 95% confidence intervals for risk of death after laparoscopy after adjustment for confounding by elevated CA-125. We considered scenarios in which the prevalence of elevated CA-125 varied from 50-80% among women undergoing laparotomy and 0-80% among women who underwent laparoscopy. We found no scenarios in which adjustment for this confounder altered our conclusions about the lack of association of laparoscopic staging with survival.

Adjusted hazard ratios and 95% confidence intervals for risk of death after laparoscopy, after adjustment for suboptimal staging and among women who did not receive adjuvant chemotherapy, are tabulated in Appendix Table 3. We considered scenarios in which the prevalence of this unmeasured confounder varied from 10-40% among women undergoing laparotomy and 10-45% among women who underwent laparoscopy. When suboptimal staging was assumed to be much more frequent among women who underwent laparoscopy, adjustment for this confounder suggested that laparoscopic staging was associated with improved survival.

Appendix Figure A.

Absolute standardized differences in variables included in propensity score before (solid diamonds) and after (hollow circles) propensity score matching. Groups are considered well balanced on a covariate when the absolute standardized difference is less than 10%.

Appendix Table A

Histologic types of epithelial ovarian cancer.

Histologic Type	ICD-O-3 code
Serous carcinoma	8441, 8460-8463
Mucinous carcinoma	8470-8471, 8480,8481
Endometrioid carcinoma	8380-8381
Clear-cell carcinoma	8310, 8313
Other Adenocarcinoma	8050, 8140, 8144, 8255, 8260, 8263, 8290, 8320, 8323, 8340, 8440, 8450, 8490, 8560, 8574, 8940

ICD-O-3 *International Classification of Disease for Oncology, Third Edition*

Appendix Table B

Point estimates and 95% confidence intervals for the relative hazard of death associated with laparoscopic staging after adjustment for elevated CA-125 under a range of assumptions about the prevalence of this potential confounder.

	Prevalence of elevated CA-125 among women undergoing laparotomy			
Prevalence of elevated CA-125 among women undergoing laparoscopy	50%	60%	70%	80%
0%	1.09 (0.76-1.54)	1.14 (0.79-1.61)	1.19 (0.83-1.69)	1.25 (0.87-1.76)
10%	1.02 (0.71-1.44)	1.07 (0.74-1.51)	1.12 (0.78-1.59)	1.17 (0.81-1.66)
20%	0.96 (0.67-1.36)	1.01 (0.70-1.43)	1.06 (0.73-1.49)	1.10 (0.77-1.56)
30%	0.91 (0.63-1.29)	0.95 (0.66-1.35)	1.00 (0.69-1.41)	1.04 (0.73-1.48)
40%	0.86 (0.60-1.22)	0.90 (0.63-1.28)	0.95 (0.66-1.34)	0.99 (0.69-1.40)
50%	0.82 (0.57-1.16)	0.86 (0.60-1.22)	0.90 (0.63-1.27)	0.94 (0.65-1.33)
60%		0.82 (0.57-1.16)	0.86 (0.58-1.21)	0.90 (0.62-1.27)
70%			0.82 (0.57-1.16)	0.86 (0.60-1.21))
80%				0.82 (0.57-1.16))

Values < 1 indicate better survival after laparoscopic staging. Values > 1 reflect better survival after staging by laparotomy.

Appendix Table C

Point estimates and 95% confidence intervals for the relative hazard of death associated with laparoscopic staging after adjustment for suboptimal staging in women who did not receive chemotherapy under a range of assumptions about the prevalence of this potential confounder.

	Prevalence of suboptimal staging in women who did not receive chemotherapy among women stage by laparotomy			
Prevalence of suboptimal staging in women who did not receive chemotherapy among staged laparoscopically	10%	20%	30%	40%
10%	0.82 (0.57-1.16)			
20%	0.73 (0.51-1.04)	0.82 (0.57-1.16)		
30%	0.67 (0.46-0.94)	0.74 (0.52-1.05)	0.82 (0.57-1.16)	
40%	0.61 (0.42-0.86)	0.68 (0.47-0.96)	0.75 (0.52-1.06)	0.82 (0.57-1.16)
45%	0.58 (0.41-0.83)	0.65 (0.45-0.92)	0.72 (0.50-1.02)	0.79 (0.55-1.11)

Values < 1 indicate better survival after laparoscopic staging. Values > 1 reflect better survival after staging by laparotomy. Bold values are significant at $p < 0.05$.

Appendix References

1. Paramasivam S, Tripcony L, Crandon A, et al. Prognostic importance of preoperative CA-125 in International Federation of Gynecology and Obstetrics stage I epithelial ovarian cancer: an Australian multicenter study. *J Clin Oncol* 23:5938-5942, 2005
2. Trimbos JB, Vergote I, Bolis G, Vermorken JB, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy In Ovarian Neoplasm trial. *J Natl Cancer Inst* 95: 113-25, 2003
3. Lin DY, Psaty BM, Kronmal RA: Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 54: 948-963, 1998

References

1. Schorge JO, Clark RM, Lee SI, Penson RT. Primary debulking surgery for advanced ovarian cancer: are you a believer or a dissenter? *Gynecol Oncol.* 2014; 135:595-605. [PubMed: 25316177]
2. Cannistra SA. Cancer of the ovary. *N Engl J Med.* 2004; 351:2519-2529. [PubMed: 15590954]
3. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. *Lancet.* 2009; 374:1371-1382. [PubMed: 19793610]

4. Iglesias DA, Ramirez PT. Role of minimally invasive surgery in staging of ovarian cancer. *Curr Treat Options Oncol*. 2009; 12:217–229.
5. Nezhat FR, Pejovic T, Finger TN, Khalil SS. Role of minimally invasive surgery in ovarian cancer. *J Minim Invasive Gynecol*. 2013; 20:754–765. [PubMed: 24183269]
6. Nezhat FR, Ezzati M, Chuang L, et al. Laparoscopic management of early ovarian and fallopian tube cancers: surgical and survival outcome. *Am J Obstet Gynecol*. 2009; 200:83.e1–83.e6. [PubMed: 19019337]
7. Tozzi R, Kohler C, Ferrara A, Schneider A. Laparoscopic treatment of early ovarian cancer: surgical and survival outcomes. *Gynecol Oncol*. 2004; 93:199–203. [PubMed: 15047236]
8. Ghezzi F, Cromi A, Siesto G, et al. Laparoscopy staging of early ovarian cancer: our experience and review of the literature. *Int J Gynecol Cancer*. 2009; 19:S7–S13. [PubMed: 19955918]
9. Ghezzi F, Cromi A, Uccella S, et al. Laparoscopy versus laparotomy for the surgical management of apparent early stage ovarian cancer. *Gynecol Oncol*. 2007; 105:409–413. [PubMed: 17275077]
10. Park JY, Kim DY, Suh DS, et al. Comparison of laparoscopy and laparotomy in surgical staging of early-stage ovarian and fallopian tubal cancer. *Ann Surg Oncol*. 2008; 15:2012–2019. [PubMed: 18437497]
11. Chi DS, Abu-Rustum NR, Sonoda Y, et al. The safety and efficacy of laparoscopic surgical staging of apparent stage I ovarian and fallopian tube cancers. *Am J Obstet Gynecol*. 2005; 192:1614–1619. [PubMed: 15902166]
12. Gallotta V, Ghezzi F, Vizza E, et al. Laparoscopic staging of apparent early stage ovarian cancer: results of a large, retrospective, multi-institutional series. *Gynecol Oncol*. 2014; 135:428–434. [PubMed: 25230214]
13. Lawrie TA, Medeiros LR, Rosa DD, et al. Laparoscopy versus laparotomy for FIGO stage I ovarian cancer. *Cochrane Database Syst Rev*. 2013; 2 CD005344.
14. Raval MV, Bilimoria KY, Stewart AK, Bentrem DJ, Ko CY. Using the NCDB for cancer care improvement: an introduction to available quality assessment tools. *J Surg Oncol*. 2009; 99:488–90. [PubMed: 19466738]
15. Edge, SE, Burd, DrCompton, CC., et al., editors. *AJCC Cancer Staging Manual* (ed 7). New York, NY: Springer; 2009.
16. Fritz, A, Percy, C, Jack, A., et al., editors. *International Classification of Diseases for Oncology* (ed 3). Geneva, Switzerland: World Health Organization; 2000.
17. Klabunde CN, Potosky AL, Legler JM, et al. Development of a comorbidity index using physician claims data. *J Clin Epidemiol*. 2000; 53:1258–1267. [PubMed: 11146273]
18. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–383. [PubMed: 3558716]
19. United States Census Bureau. Census Regions and Divisions of the United States. www.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf
20. United States Department of Agriculture Economic Research Service: Rural Urban Continuum Codes. <http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx>
21. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983; 70:41–55.
22. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2001; 10:150–161.
23. Ho DE, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. *Journal of Statistical Software*. 2011; 42:1–28. Available online at <http://www.jstatsoft.org/v42/i08/>.
24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009; 28:3083–3107. [PubMed: 19757444]
25. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics*. 1998; 54:948–963. [PubMed: 9750244]

26. Paramasivam S, Tripcony L, Crandon A, et al. Prognostic importance of preoperative CA-125 in International Federation of Gynecology and Obstetrics stage I epithelial ovarian cancer: an Australian multicenter study. *J Clin Oncol.* 2005; 23:5938–5942. [PubMed: 16087942]
27. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy In Ovarian Neoplasm trial. *J Natl Cancer Inst.* 2003; 95:113–125. [PubMed: 12529344]
28. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol.* 2009; 27:5331–5336. [PubMed: 19805679]
29. Kornblith AB, Huang HQ, Walker JL, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. *J Clin Oncol.* 2009; 27:5337–5342. [PubMed: 19805678]
30. Angioli R, Plotti F, Palaia I, et al. Update on lymphadenectomy in early and advanced ovarian cancer. *Curr Opin Obstet Gynecol.* 2008; 20:34–39. [PubMed: 18197003]
31. Spirtos NM, Eisekop SM, Boike G, Schlaerth JB, Cappellari JO. Laparoscopic staging in patients with incompletely staged cancers of the uterus, ovary, fallopian tube, and primary peritoneum: a Gynecologic Oncology Group (GOG) study. *Am J Obstet Gynecol.* 2005; 193:1645–1649. [PubMed: 16260204]
32. Patel PR, Lee J, Rodriguez AM, Borahay MA, et al. Disparities in Utilization of Laparoscopic Hysterectomies: A Nationwide Analysis. *J Minim Invasive Gynecol.* 2014; 21:223–227. [PubMed: 24012920]
33. Varela JE, Nguyen NT. Disparities in access to basic laparoscopic surgery at U.S. academic medical centers. *Surg Endosc.* 2011; 25:1209–1214. [PubMed: 20848139]
34. Winchester DP, Stewart AK, Phillips JL, Ward EE. The National Cancer Data Base: Past, Present, and Future. *Ann Surg Oncol.* 2010; 17:4–7. [PubMed: 19847564]

Figure 1.

Flow diagram of the study population and propensity matched cohort. Exclusion criteria are described on right hand side. Utilizing an optimal algorithm to perform 1:1 propensity score matching, 1,096 patients who underwent laparoscopy were successfully matched to a patient who underwent laparotomy.

No. of patients at risk

Laparotomy	1030	986	888	712	523	353	201	99
Laparoscopy	1053	999	889	711	506	345	193	88

Figure 2.

Kaplan-Meier plot of overall survival in the propensity matched cohort, p value based on the log rank test.

Table 1
Characteristics of patients undergoing staging of presumed stage I epithelial ovarian cancer surgical approach before and after propensity score matching

Characteristic	All subjects (n = 4,798)		Propensity score matched cohort ^a (n = 2,192)	
	Laparoscopy (n = 1,112)	Laparotomy (n = 3,686)	Laparoscopy (n = 1,096)	Laparotomy (n = 1,096)
Median age at diagnosis, years (interquartile range)	56.5 (49-65)	57 (50-64)	57 (49-65)	57 (50-65)
Race/ethnicity				
Black	44 (4.0) ^c	207 (5.6)	44 (4.0)	45 (4.1)
Hispanic	37 (3.3)	204 (5.5)	37 (3.4)	38 (3.5)
White	960 (86.3)	2,984 (81.0)	944 (86.1)	949 (86.6)
Other	59 (5.3)	253 (6.9)	59 (5.4)	53 (4.8)
Unknown	12 (1.1)	38 (1.0)	12 (1.1)	13 (1.2)
Facility type				
Academic/research program	470 (42.3)	1,773 (48.1)	469 (42.8)	451 (41.1)
Community cancer program	45 (4.0)	115 (3.1)	43 (3.9)	36 (3.3)
Comprehensive community cancer program	502 (45.1)	1,479 (40.1)	491 (44.8)	497 (45.3)
Integrated network cancer program	92 (8.3)	310 (8.4)	91 (8.3)	109 (9.9)
Other	3 (0.3)	9 (0.2)	2 (0.2)	3 (0.3)
Area of residence				
Urban	1,071 (96.3)	3,512 (95.3)	1,055 (96.3)	1,055 (97.2)
Rural	12 (1.1)	52 (1.4)	12 (1.1)	10 (0.9)
Unknown	29 (2.6)	122 (3.3)	29 (2.6)	31 (2.8)
Region				
Northeast	281 (25.3)	754 (20.5)	272 (24.8)	259 (23.6)
Midwest	254 (22.8)	995 (27.0)	253 (23.1)	253 (23.1)
South	378 (34.0)	1,208 (32.8)	372 (33.9)	388 (35.4)
West	199 (17.9)	729 (19.8)	199 (18.2)	196 (17.9)
Median household income of zip code of residence				

Characteristic	All subjects (n = 4,798)			Propensity score matched cohort ^a (n = 2,192)	
	Laparoscopy (n = 1,112)	Laparotomy (n = 3,686)	p-value	Laparoscopy n = 1,096	Laparotomy n = 1,096
Less than \$38,000	96 (8.6)	484 (13.1)		96 (8.8)	95 (8.7)
\$38,000-\$47,999	212 (19.1)	738 (20.0)		209 (19.1)	217 (19.8)
\$47,000-\$62,999	308 (27.7)	1,018 (27.6)		303 (27.6)	310 (28.3)
\$63,000 or more	490 (44.1)	1,431 (38.8)		483 (44.1)	469 (42.8)
Unknown	6 (0.5)	15 (0.4)		5 (0.5)	5 (0.5)
Insurance status at diagnosis					
Private	744 (66.9)	2,309 (62.6)		731 (66.7)	733 (66.9)
Medicare	277 (24.9)	875 (23.7)		274 (25.0)	280 (25.5)
Other Government	34 (3.1)	245 (6.6)		34 (3.1)	28 (2.6)
None	44 (4.0)	202 (5.5)		44 (4.0)	41 (3.7)
Unknown	13 (1.2)	55 (1.5)		13 (1.2)	14 (1.3)
Number of comorbidities					
0	939 (84.4)	2,990 (81.1)		923 (84.2)	924 (84.3)
1	151 (13.6)	609 (16.5)		151 (13.8)	148 (13.5)
2 or more	22 (2.0)	87 (2.4)		22 (2.0)	24 (2.2)
Histological type					
Endometrioid carcinoma	1,352 (28.2)	324 (29.1)		321 (29.3)	303 (27.6)
Serous carcinoma	319 (28.7)	892 (24.2)		314 (28.6)	301 (27.5)
Mucinous carcinoma	123 (11.1)	645 (17.5)		121 (11.0)	169 (15.4)
Clear cell carcinoma	195 (17.5)	682 (18.5)		193 (17.6)	192 (17.5)
Other Adenocarcinoma	151 (13.6)	439 (11.9)		147 (13.4)	131 (12.0)
Histological grade					
1	201 (18.1)	689 (18.7)		198 (18.1%)	193 (17.6%)
2	210 (18.9)	756 (20.5)		207 (18.9%)	206 (18.8%)
3	632 (56.8)	1,987 (53.9)		623 (56.8%)	621 (56.7%)
Unknown	69 (6.2)	254 (6.9)		68 (6.2%)	76 (6.9%)
Tumor size					

Characteristic	All subjects (n = 4,798)			Propensity score matched cohort ^a (n = 2,192)		
	Laparoscopy (n = 1,112)	Laparotomy (n = 3,686)	p-value	Laparoscopy n = 1,096	Laparotomy n = 1,096	p-value
Smaller than 1 cm	60 (5.4)	160 (4.3)		60 (5.4)	62 (5.7)	
1.0-4.9 cm	224 (20.1)	440 (11.9)		218 (19.9)	222 (20.2)	
5.0-9.9 cm	302 (27.2)	605 (16.4)		292 (26.6)	308 (28.1)	
10 cm or larger	382 (34.4)	2,096 (56.9)		382 (34.6)	376 (34.3)	
Unknown	144 (12.9)	385 (10.4)	0.37 ^d	144 (13.1)	128 (11.7)	0.27 ^d
Adjuvant chemotherapy						
No	427 (38.4)	1,429 (38.8)		419 (38.2)	404 (36.9)	
Yes	608 (54.7)	2,044 (55.5)		600 (54.7)	630 (57.5)	
Unknown	77 (6.9)	213 (5.8)		77 (7.0)	62 (5.7)	

^aPropensity score model included age, race/ethnicity, facility type, year of diagnosis, area of residence, region, median household income of zip code of residence, insurance status, comorbidities, and tumor size.

^bWilcoxon rank sum test

^cAll cells are counts with percentages in parentheses unless otherwise stated

^d χ^2 test

Table 2
Surgical and survival outcomes by mode of surgery in propensity score matched cohort

Outcome	Laparoscopy (n=1,096)	Laparotomy (n=1,096)	p-value
Median follow up, months (95%) ^a	28.7 (20.4-38.9)	29.3 (20.6-39.3)	0.77 ^b
Survival probability, percent (95% CI) ^a			
3 years	94.1 (92.4-95.8)	92.4 (90.4-94.3)	0.19 ^c
4 years	91.5 (89.0-94.1)	88.5 (85.3-91.9)	0.17 ^c
Length of postoperative admission (days), median (IQR)	3 (1-4)	4 (3-5)	<0.001 ^d
Unplanned readmission within 30 days of surgical discharge, percent (95% CI) ^e	2.8 (2.0-4.0)	3.9 (2.9-5.2)	0.37 ^f
Death within 90 days of surgery, percent (95% CI) ^g	0.3 (0-0.9)	0.9 (0.4-1.7)	0.10 ^f
Lymph node count, median (IQR)	14 (7-22)	12 (6-20)	0.005 ^d

CI: Confidence interval IQR: Intraquartile range

^aCalculated using the Kaplan-Meier method

^bLog rank test

^cZ-test for independent proportions

^dWilcoxon rank sum test

^eUnknown for eight subjects, who were excluded from the analysis

^f χ^2 test

^gUnknown for 42 subjects, who were excluded from the analysis