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SECONDARY SURGERY VS CHEMOTHERAPY FOR RECURRENT OVARIAN CANCER

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Abstract

Objective—The best course of treatment for recurrent ovarian cancer is uncertain. We sought to determine whether secondary cytoreductive surgery for first recurrence of ovarian cancer improves overall survival compared to other treatments.

Methods—We assessed survival using Surveillance, Epidemiology and End Results-Medicare data for advanced stage ovarian cancer cases diagnosed from January 1, 1997- December 31, 2007 with survival data through 2010 using multinomial propensity weighted finite mixture survival regression models to distinguish true from misclassified recurrences. Of 35,995 women ages 66 years and older with ovarian cancer, 3439 underwent optimal primary debulking surgery with 6 cycles of chemotherapy; 2038 experienced a remission.

Results—1635 out of 2038 (80%) women received treatment for recurrence of whom 72% were treated with chemotherapy only, 16% with surgery and chemotherapy and 12% received hospice care. Median survival of women treated with chemotherapy alone, surgery and chemotherapy, or hospice care was 4.1 years, 5.4 years, and 2.2 years, respectively ($p < 0.001$). Of those receiving no secondary treatments, 75% were likely true nonrecurrences with median survival of 15.9 years and 25% misclassified with 2.4 years survival. Survival among women with recurrence was greater for those treated with surgery and chemotherapy compared to chemotherapy alone (HR=1.67; 95% confidence interval: 1.13–2.47). Women who were older with more comorbidities and high grade cancer had worse survival.

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Conclusions—Secondary surgery with chemotherapy to treat recurrent ovarian cancer increases survival by 1.3 years compared to chemotherapy alone and pending ongoing randomized trial results, may be considered a standard of care.

Keywords

recurrent ovarian cancer; SEER-medicare; secondary surgery; survival

Background

The majority of ovarian cancers are diagnosed at late stage and initially respond to platinum-based chemotherapy; unfortunately most recur.^[1] For women experiencing recurrent ovarian cancer, the best course of treatment is uncertain. Typically, recurrent cancer is treated with chemotherapy but starting in the early 1990s, secondary cytoreductive surgery (SCS) appeared as a treatment option.^[2] By 1996, the National Comprehensive Cancer Network guidelines incorporated SCS as a treatment choice along with chemotherapy despite lack of randomized trial data of its efficacy.^[3] A recent Cochrane review of secondary surgery for recurrent epithelial ovarian cancer concludes that existing findings are inconclusive.^[4] Most of the studies were single institutional case reports and few reported survival comparing surgery with chemotherapy. No study was population-based. As 46% of ovarian cancer cases occurred in women 65 years and older,^[1] SEER Medicare data offers an opportunity to assess survival benefits of secondary surgery over chemotherapy alone. However, such explorations have been hampered by the limitations of administrative data – lack of specific procedure codes for recurrences or SCS, the challenge of identifying recurrent cancer, a condition without a specific diagnostic code. While evidence of a second round of surgery may be used to identify recurrences, this approach has the potential to misclassify untreated patients as nonrecurrence. Additionally, there is the inherent observational bias of healthier individuals receiving more aggressive treatments. Randomized trials comparing chemotherapy with secondary surgery are underway but results are years away. To help inform decision-making for women with recurrent ovarian cancer, we performed a population-based analysis of secondary surgical treatment compared with chemotherapy and with hospice using doubly robust regression methods, a novel multiple treatment propensity score methods to account for selection into treatment, and finite mixture survival models to account for potential misclassification of nonrecurrence.

Methods

Cohort Selection

We used linked SEER-Medicare data for ovarian cancer cases diagnosed from January 1, 1997- December 31, 2007 with claims and mortality data through 2010 (N=35,995). We excluded women with more than one primary cancer (N=5806), nonepithelial ovarian cancer cases (N=871), those diagnosed prior to 1997 (N=956) as well as women who received the diagnosis at autopsy or on death certificate (N=16). We excluded women not enrolled in both Medicare parts A (inpatient) and B (outpatient) and those enrolled in a health maintenance organization (N=4150) as they do not have complete Medicare fee-for-service claims. We also excluded women with early stage cancer (N=10,952) who have a low

likelihood of recurrence. Because we aimed to assess the effect of secondary debulking surgery for recurrent cancer, we included only who had undergone primary debulking for their primary ovarian cancer treatment. As we aimed to assess the comparative effectiveness of secondary surgery vs chemotherapy for recurrence, we included those treated optimally for their primary ovarian cancer, meaning those who underwent primary surgery and chemotherapy. Finally, we limited the analyses to women ≥ 66 years (N=5310) to capture comorbidities during the year prior to cancer diagnosis.

Identifying secondary surgery and first recurrence

We obtained codes used by gynecologic oncology billers from centers in the Northeast, mid-Atlantic, Southeast, Midwest, Southwest, Pacific and Pacific Northwest (list in Appendix 1) for SCS. A chart validation of these codes revealed a sensitivity of 77% and specificity of 92%.^[5] To identify recurrent cancer, we created an algorithm based on expert gynecologic oncology opinion and the literature^[4,6,7] that incorporates timing and utilization of either secondary surgery or chemotherapy. Recurrent cancer was defined by the presence of claims for secondary surgery, chemotherapy or hospice following a 180-day treatment free window after completion of primary course of therapy to distinguish between recurrent and persistent disease. We used diagnosis (ICD9) and procedure (CPT/Medicare HCPCS) codes for chemotherapy regimens commonly administered for recurrent ovarian cancer culled from gynecologic oncology billers (see Appendix 2). Chart validation of a diagnosis recurrent ovarian cancer using this algorithm yielded a sensitivity of 100% and specificity of 89%.^[5]

Treatment

We identified primary treatment searching Medicare claims from 30 days prior to 120 days after the date of diagnosis. Since SEER reports only month and year of the diagnoses, the diagnosis date was assigned the 15th day of the month. We identified primary surgical treatment in inpatient files using ICD-9 procedure and outpatient and physician files using HCPCS codes, and receipt of chemotherapy using inpatient, outpatient, physician claims, and DME (Durable Medical Equipment) files. Primary chemotherapy was the first chemotherapy that occurred within 180 days prior to and 90 days after surgical treatment. Chemotherapy claims from all sources within three days were grouped into one. To distinguish between persistent and recurrent cancer, there had to be a 6 month treatment-free window following completion of primary treatment.

Treatment Groups

We classified treatment for recurrent cancer into 4 categories: secondary surgery (with or without chemotherapy), chemotherapy only, hospice, no treatment. A small number of women (N=26) appear to have had secondary surgery without chemotherapy. In preliminary analysis we dropped these observations from the analysis sample. As there were no substantive differences between this and our final sample in terms of means of explanatory variables or treatment effects, we included them with secondary surgery and chemotherapy group.

Sociodemographic and clinical variables

Age, race, SEER geographic region, year of diagnosis, tumor grade, histology and stage are from SEER. We used median household income of the woman's residence zipcode. We assessed comorbidity using Elixhauser⁸ and Charlson⁹ indices to take into account both risk of in-hospital and longer term mortality and used comorbidities identified in inpatient and outpatient claims in the year prior to diagnosis of cancer.

Outcome

Overall survival was measured from the 15th day of the month of diagnosis to the date of death from any cause as reported in the Medicare database. Observations were censored at 12/31/2010, the last recorded date of follow-up in Medicare records.

Statistical Analysis

We use propensity score methods for multiple treatments^[10] to minimize bias from selection into treatment. We estimate a multinomial logit model of treatments controlling for relevant socioeconomic and clinical characteristics such as age, race, income, stage, histology, comorbidity, diagnosis year and SEER region to predict type of treatment (surgery, chemotherapy, hospice, none) received. We use the estimated parameters to create inverse propensity score weights.

We use finite mixture log logistic survival models to assess the association of type of therapy with survival while controlling for propensity scores using inverse probability weighting.

The survival models also control for socioeconomic and clinical characteristics, thus the treatment effects obtained are doubly robust.^[11] Finite mixture models allow for estimation of survival differences between treatment groups while differentiating the truly nonrecurrent cases from those women who did experience a recurrence but were misclassified because they did not receive SCS, chemotherapy or hospice care. Finite mixture models have been used to model cancer survival,^[12,13] and have many applications in other areas of health services, biology, marketing, and engineering.^[14–17] This approach distinguishes between individuals with a greater probability to be in one group as compared to another, such as those with longer vs. shorter survival.

Parametric survival analyses were used to identify distributions that provided the best fit to the data. Commonly used distributions including exponential, Weibull, log-normal and log-logistic curves were tested, and the fit of each was assessed by using the Akaike information criterion (AIC) criterion. These analyses showed that a log-logistic survival model fit the data best. The estimated parametric survival curves were also very close to observed Kaplan–Meier curves. Therefore, we used log-logistic distributions to construct the finite mixture model of survival allowing for two classes (types) of observations. Both the class probability and determinants of survival for each class (including effect of treatment) were estimated simultaneously using inverse propensity score weighted maximum likelihood.

Results

Of the 7934 women, 3439 underwent primary cytoreductive surgery and chemotherapy, standard optimal treatment for a new ovarian cancer. Of these, 1401 had persistent cancer, defined as receiving treatment for ovarian cancer within 6 months of completing their primary treatment, and were excluded. The final sample included 2038 women (See CONSORT Figure 1).

Treatments

Table 1 shows the characteristics of women by treatment status in the sample and also weighted by the inverse propensity score obtained from multinomial logit regressions. Propensity weighted analyses resulted in similarly matched groups. Of the 1635 women who experience recurrence, 16% were treated with SCS and chemotherapy, 72% with chemotherapy alone and 12% received hospice care. Younger women and those with fewer comorbidities were more likely to undergo surgery. There was no racial difference in treatment receipt. There was geographic variation with higher rates of SCS in the West. On average, women enrolled in hospice were older, had more comorbidities and were more likely to have metastatic disease. Women in the no treatment/no recurrence group tended to be younger, less likely to have stage 4 and have a slightly higher income. Year of diagnosis was not associated with treatment type and rates of SCS did not increase during the 1997 to 2007 time period ($p=0.33$) (see Table 2). Although there are numerous statistically significant differences in baseline characteristics across treatments in the sample, these differences become much smaller and always statistically insignificant once the sample is weighted using inverse propensity score weights (Table 1). While there was a statistically significant difference in median time from diagnosis to recurrence between women treated for recurrence with chemotherapy vs surgery (643d vs 694d; $p=0.007$), there remains a significant difference in time between recurrence and death for those treated with chemotherapy vs surgery (660d vs 1097d; $p<0.0001$).

Survival Analyses

Actual survival is shown in Figure 2. Survival for women who underwent secondary debulking with chemotherapy was better compared to those who received chemotherapy only. In both unadjusted for propensity of treatment and propensity weighted analyses, treatment type, and younger age were associated with improved survival (Table 3). Propensity score adjusted log logistic analyses showed that women undergoing surgery with chemotherapy had significantly greater survival compared to those receiving chemotherapy alone (hazard ratio [HR]: 1.33, 95% confidence interval [CI]: 1.20, 1.47). Women receiving no secondary treatment, classified as nonrecurrent, had significantly better survival (HR: 2.33, 95% CI: 1.97, 2.76), while women in hospice had significantly lower survival than those who underwent chemotherapy alone (HR=0.55, 95% CI: 0.51, 0.59). The estimated median survival of women treated with chemotherapy was 4.1 years from time of diagnosis; 77% of this group died within the study period. Those treated with secondary surgery and chemotherapy survived a median of 5.4 years; 67% died. Those receiving hospice survived an average of 2.2 years; 99% died. The 403 women who received no secondary treatments

were classified as nonrecurrent and had a median survival of 9.3 years; 19.6% died (see Figure 3).

However, the group that received no secondary treatments and was classified as nonrecurrent, likely included women who were truly nonrecurrent and those with recurrence who went untreated and were misclassified. Estimation of a 2-class finite mixture log-logistic survival model, including the factors listed in Table 1, identified two distinct classes of women with different survival (Table 3) with associated class probabilities of 75% (95% CI: 62, 85%) and 25% (95% CI: 18, 35%), respectively. The survival ratios, relative to chemotherapy, for observations in the two classes are 3.91 (95% CI: 2.88,5.31) for the truly nonrecurrent and 0.57 (95% CI: 0.42,0.78) for those misclassified as nonrecurrent who went untreated. Survival ratios for chemotherapy and surgery and for hospice are not significantly different across the two classes and are qualitatively very similar to those obtained from the standard log-logistic survival model described above. However, survival ratios for the no-treatment group is significantly different between the log logistic and finite mixture models (HR=2.3 vs 3.9 vs 0.57; $p<0.000$). Median survival was 15.9 years for the truly nonrecurrent with longer survival as compared to 2.4 years in the group misclassified as nonrecurrent, those with shorter survival (Figure 3). Of the untreated women who were likely misclassified as nonrecurrent cancer, 55% listed cancer as their cause of death.

Most of the control covariates were not statistically significant determinants of survival. However, women with more comorbidities, higher grade cancer or older had worse survival (Table 3).

Discussion

Ovarian cancer patients are living longer than they did 30 years ago with 5 year survival rates increasing from 20% to 40%.^[19,20] While some of the improved survival is likely due to platinum-based therapies, the role of secondary surgery in improving survival has been uncertain. Many case studies and a recent Cochrane review suggest its effectiveness^[4] but there has not been a population based study that takes into account the potential observational biases inherent in cohort studies.^[20] Our population-based findings suggest that treating first recurrence of ovarian cancer with secondary surgery and chemotherapy increases survival by >1 year compared to chemotherapy alone. While randomized controlled trial data are the gold standard for assessing treatment efficacy, eligibility limitations often make it difficult to apply findings to broader populations, particularly the elderly. Comparing effectiveness of treatments using population-based data can help inform physician and patient decision-making pending results of ongoing randomized phase 3 trials.^[18] Our findings pertain to women 66 years and older who represent a substantial portion of ovarian cancer in the US. Yet, we expect these findings may be useful for younger women who tend to have less comorbidity and may be better surgical candidates.

Our finding of less aggressive treatments among older and sicker patients is consistent with the literature of primary treatment of ovarian cancer.^[21–25] While others have described a racial disparity in primary treatment of ovarian cancer,^[21,26,27] we did not see this pattern

for secondary treatments, perhaps because we limited this analysis to those patients who received optimal primary therapy.

A key challenge to evaluating the effectiveness of secondary treatments lies in the difficulty of accurately identifying secondary surgery and recurrent cancer. We approached and overcame these challenges with 2 methods – the first, a chart validation study that yielded excellent sensitivity and specificity of the coding algorithm. Although the algorithm was based on data billing codes from across the country and appears accurate, it was validated using a single institution's charts and may not work as well in other settings. Secondary surgery codes are further confounded by second look procedures which, despite improvements in imaging techniques, continue to be done to ensure that no lesions remain. This surgery can include removal of tissue for pathologic review which can be for diagnostic and treatment purposes. Because the vast majority of secondary surgeries in our cohort were accompanied by chemotherapy, it is unlikely that there was much misclassification. Similarly, we may have misclassified women with persistent cancer as they may have been receiving ongoing maintenance therapy. We believe such misclassification is unlikely since this group had a shortened median survival time (1.6 years), which is consistent with persistent disease. In addition, to further maximize our ability to assess effectiveness of secondary surgery for recurrent disease, we excluded women with persistent disease – those who continued to receive chemotherapy beyond the usual 6 months post-primary surgery. That our sample included only 265 women undergoing secondary surgery yet finds significant survival differences suggests the potential strength of the association found. Rates of performance may differ in a younger population. As with all administrative claims based analyses, our findings are limited by the inherent unmeasured biases of observational data. We used standard inverse propensity weighted analytic methods to reduce the impact of such biases, but may not eliminate them.

We recognize the inherent difficulty of classifying recurrent cancer by the presence of claims for treatment. Particularly in an elderly population, many women will go untreated when cancer recurs resulting in distorted survival estimates. To counter this challenge, we used finite mixture models, a novel approach to separate out the truly nonrecurrent from those with recurrence who forego active or hospice treatment. By utilizing this approach with persistent cancer, we obtain more accurate measures of survival among women who truly did not experience a recurrence, a count that is not obscured by the inclusion of those with recurrence who went untreated.

In summary, for women with advanced ovarian cancer initially treated with surgery and chemotherapy who experience a recurrence, secondary cytoreductive surgery with chemotherapy appears to provide a significant survival advantage over chemotherapy alone and may be considered a standard of care pending results of ongoing randomized trials.

Acknowledgments

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Appendix 1. ICD9, HCPCS, CPT codes for ovarian cancer surgery

Surgery

ICD 9 Procedure Codes with or without a diagnosis of ovarian cancer

65.31- Lap Unilat Oophorectomy
65.39- Oth Unilat Oophorectomy
65.41- Lap Uni Salpingo-Oophor
65.49- Oth Uni Salpingo-Oophor
65.51- Oth Remove Both Ovaries
65.52- Oth Remove Remain Ovary
65.53- Lap Remove Both Ovaries
65.54- Lap Remove Remain Ovary
65.61- Oth Remove Ovaries/Tubes
65.62- Oth Remove Rem Ova/Tube
65.63- Lap Remove Ovaries/Tubes
65.64- Lap Remove Rem Ova/Tube

ICD9 procedure codes only with a diagnoses of ovarian cancer (183.XX):

40.3X- Regional lymph node excision
40.5X- Radical excision of other lymph nodes
54.3X- Excision/destruction abdominal wall lesion
54.4X- Omentectomy, excision, destruction of the peritoneal tissue
68.3X- Subtotal Abdominal Hysterectomy
68.4X- Total Abdominal Hysterectomy
68.5X- Vaginal Hysterectomy
68.6X- Radical Abdominal Hysterectomy
68.7X- Radical Vaginal Hysterectomy
68.8X- Pelvic Evisceration
68.9X- Other and Unspecified Hysterectomy
70.32- Excision/destruction cul de sac lesion

HCPCS codes with or without a diagnosis of ovarian cancer:

58180- Supracervical abdominal hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary

58200- Total abdominal hysterectomy, including partial vaginectomy, with para-aortic and pelvic lymph node sampling, with or without removal of tube(s), with or without removal of ovary(s)

58210- Radical abdominal hysterectomy, with bilateral total pelvic lymphadenectomy and para-aortic lymph node sampling (biopsy) with or without removal of tube(s), with or without removal of ovary(s)

58940- Oophorectomy, partial or total, unilateral or bilateral

58943- Oophorectomy, partial or total, unilateral or bilateral; for ovarian, tubal or primary peritoneal malignancy, with para-aortic and pelvic lymph node biopsies, peritoneal washings, peritoneal biopsies, diaphragmatic assessments, with or without salpingectomy(s), with or without omentectomy

58950- Resection (initial) of ovarian, tubal or primary peritoneal malignancy with bilateral salpingo-oophorectomy and omentectomy

58951- Resection of ovarian, tubal or primary peritoneal malignancy with bilateral salpingo-oophorectomy and omentectomy; with total abdominal hysterectomy, pelvic and limited para-aortic lymphadenectomy

58952- Resection of ovarian, tubal or primary peritoneal malignancy with bilateral salpingo-oophorectomy and omentectomy; with radical dissection for debulking (ie, radical excision or destruction, intra-abdominal or retroperitoneal tumors)

58953- Bilateral salpingo-oophorectomy with omentectomy, total abdominal hysterectomy and radical dissection for debulking

58954- Bilateral salpingo-oophorectomy with omentectomy, total abdominal hysterectomy and radical dissection for debulking; with pelvic lymphadenectomy and limited para-aortic lymphadenectomy

58956- Total abdominal hysterectomy, BSO with malignancy

HCPCS codes with a diagnosis of ovarian cancer (183.XX):

38562- Limited lymphadenectomy for staging (separate procedure)

38570- Laparoscopy, surgical; with retroperitoneal lymph node sampling (biopsy) single or multiple

38571- Laparoscopy, surgical; with bilateral total pelvic lymphadenectomy

38572- Laparoscopy, surgical; with bilateral total pelvic lymphadenectomy and para-aortic lymph node sampling, single or multiple

44140- Colectomy

44200- Laparoscopy, surgical; enterolysis (freeing of intestinal adhesion) (separate procedure)

44950- Appendectomy

44970- Laparoscopy, surgical appendectomy

49000- Exploratory laparotomy, exploratory celiotomy with or without biopsy (s) (separate procedure)

49002- Reopening of recent laparotomy

49010- Exploration, retroperitoneal area with or without biopsy (separate procedure)

49320- Laparoscopy, abdomen, peritoneum, and omentum, diagnostic, with or without collection of specimen (s) by brushing or washing (separate procedure)

49321- Laparoscopy, surgical; with biopsy (single or multiple)

49322- Laparoscopy, surgical; with aspiration of cavity or cyst (eg. Ovarian cyst) (single or multiple)

58150- Total abdominal hysterectomy (corpus and cervix) with or without removal of tube(s), ovary(s)

58550- Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 grams or less

58552- Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 grams or less, with removal of tubes and/or ovary

58553- Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 grams

58554- Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 grams, with removal of tubes and/or ovary

58570- Laparoscopy, surgical, with total hysterectomy, for uterus 250 grams or less

58571- Laparoscopy, surgical, with total hysterectomy, for uterus 250 grams or less, with removal of tubes and/or ovary

58572- Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 grams

58573- Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 grams, with removal of tubes and/or ovary

58660- Laparoscopy, surgical; with lysis of adhesions (salpingolysis, ovariolysis) (separate procedure)

58661- Laparoscopy, surgical, with retroperitoneal lymph node sampling (biopsy) single or multiple

58662- Laparoscopy, surgical, with retroperitoneal lymph node sampling (biopsy) single or multiple

58700- Salpingectomy, complete or partial

58720- Salpingo-oophorectomy, complete or partial (separate procedure)

58925- Closure of vesicouterine fistula; with hysterectomy

58960- Laparoscopy for staging or restaging or ovarian, tubal or primary peritoneal malignancy (second look) with or without omentectomy, peritoneal washing, biopsy of abdominal and pelvic peritoneum, diaphragmatic assessment with pelvic and limited para-aorti

Appendix 2: Chemotherapy Codes

ICD9 procedure codes:

99.25- Infusion of therapeutic substance into intraperitoneal cavity

ICD9 diagnoses codes:

V58.1X- Encounter for chemotherapy and immunotherapy for neoplastic conditions

V66.2X- Convalescence and palliative care following chemotherapy

V67.2X- Follow-up examination following chemotherapy

E93.07 – body measurement

DRG code:

410-

HCPCS codes:

964XX-Administration

965XX- Administration

Q0083- Chemotherapy

Q0084- Administration

G0356- Chemo injection, sq or intramuscular, hormonal agent

G0357- Chemo IV push, single drug

G0358- Administration of each additional pushed chemo drug

G0359- Chemo IV infusion, single/initial drug, initial hour

G0360- Each additional hour of infusion (up to 8 hrs)

G0361- Initiation of prolonged chemo (>8 hrs)

G0362- Administration of each additional infused chemo drug, up to 1 hr

G9021- Chemotherapy assessment for nausea and/or vomiting, patient reported, performed at the time of chemotherapy administration; assessment level one: not at all

G9022- Chemotherapy assessment for nausea and/or vomiting, patient reported, performed at the time of chemotherapy administration; assessment level two: a little

G9023- Chemotherapy assessment for nausea and/or vomiting, patient reported, performed at the time of chemotherapy administration; assessment level three: quite a bit

G9024- Chemotherapy assessment for nausea and/or vomiting, patient reported, performed at the time of chemotherapy administration; assessment level four: very much

G9025- Chemotherapy assessment for pain, patient reported, performed at the time of chemotherapy administration, assessment level one: not at all

G9026- Chemotherapy assessment for pain, patient reported, performed at the time of chemotherapy administration, assessment level two: a little

G9027- Chemotherapy assessment for pain, patient reported, performed at the time of chemotherapy administration, assessment level three: quite a bit

G9028- Chemotherapy assessment for pain, patient reported, performed at the time of chemotherapy administration, assessment level four: very much

G9029- Chemotherapy assessment for lack of energy (fatigue), patient reported, performed at the time of chemotherapy administration, assessment level one: not at all

G9030- Chemotherapy assessment for lack of energy (fatigue), patient reported, performed at the time of chemotherapy administration, assessment level two: a little bit

G9031- Chemotherapy assessment for lack of energy (fatigue), patient reported, performed at the time of chemotherapy administration, assessment level three: quite a bit

G9032- Chemotherapy assessment for lack of energy (fatigue), patient reported, performed at the time of chemotherapy administration, assessment level four: very much

Neulasta 6 mg-

HCPCS: J2505

NDC: 54868522900, 55513019001

Topotecan-

HCPCS: J8705, J9350

NDC: 00007420101, 00007420105

Cyclophosphamide (Cytosan) 25 mg-

HCPCS: J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097

NDC: 00013560693, 00015053941, 00013561693, 00015054641, 00013562693, 00015054712, 00015054741, 10019095501, 00013563670, 00015050541, 00015054812, 00015054841, 10019095601, 38779050603, 38779050604,

38779050605, 00013564670, 00015050641, 00015054912, 00015054941,
10019095701

Etoposide (Toposar)/Etopophos/VePesid-

HCPCS: J8560, J9181

NDC: 00013733691, 00013734694, 00013735688, 00015306120, 00015306220,
00015308420, 00015309520, 00015340420, 00703565301, 00703565601,
00703565701, 10019093001, 10019093002, 55390029101, 55390029201,
55390029301, 55390049101, 55390049201, 55390049301, 63323010405,
63323010425, 63323010450

Adriamycin 10 mg-

HCPCS: J9000

NDC: 00013108691, 00013109691, 00013110679, 00013111683, 00013113691,
00013114691, 00013115679, 00013116683, 00015335222, 00015335322,
00703504001, 00703504303, 00703504601, 10019092001, 10019092102,
38779065206, 38779065209, 49452243701, 55390023110, 55390023210,
55390023301, 55390023510, 55390023610, 55390023701, 55390023801,
55390024110, 55390024210, 55390024301, 55390024510, 55390024610,
55390024701, 55390024801, 63323010161, 63323088305, 63323088310,
63323088330

Doxil 10 mg-

HCPCS: J9001

NDC: 17314960001, 17314960002

Bevacizumab (Avastin) 10 mg/Bevacizumab-

HCPCS: J9035, J9999

NDC: 50242006001, 50242006101, 50242006002

Carboplatin 50 mg/Paraplatin-

HCPCS: J9045

NDC: 00015321030, 00015321076, 00015321130, 00015321130, 00015321176,
00015321230, 00015321276, 00015321330, 00015321430, 00015321530,
00015321630, 00015323011, 00015323111, 00015323211, 00409112911,
00409112912, 00591333626, 0591333712, 00591333889, 00591345460,
00703324411, 00703324611, 00703326401, 00703326601, 00703326801,
00703326871, 00703327401, 00703327601, 00703327801, 00703424401,
00703424601, 00703424801, 10019091201, 10019091202, 10019091203,
10019091501, 10019091601, 10019091701, 10139006005, 10139006015,
10139006045, 15210006112, 15210006312, 15210006612, 15210006712,
50111096576, 50111096676, 50111096776, 55390015001, 55390015101,
55390015201, 55390015301, 55390015401, 55390015501, 55390015601,
55390022001, 55390022101, 55390022201, 61703033922, 61703033950,

61703033956, 61703036018, 61703036022, 61703036050, 63323016610,
63323016720, 63323016721, 63323016800, 63323017245, 63323017260,
67817006112, 67817006312, 67817006612, 67817006712,

Cisplatin/Platinol-

HCPCS: J9060, J9062

NDC: 00015322022, 00015322122, 00703574711, 00703574811, 10019091001,
10019091002, 49452207801, 49452207802, 49452207803, 51552107609,
55390009901, 55390011250, 55390011299, 55390018701, 55390041450,
55390041499, 63323010351, 63323010364, 63323010365, 63323010391,
63323010395

Taxotere 20 mg/Docetaxel-

HCPCS: J9170

NDC: 00075800120, 00075800180

Gemzar/Gemcitabine-

HCPCS: J9201

NDC: 00002750101, 00002750101, 00002750201

Taxol/Paclitaxel-

HCPCS: J9264, J9265

NDC: 68817013450, 00015347530, 00015347630, 00015347911, 00074433501,
00074433502, 00074433504, 00172375377, 00172375396, 00172375473,
00172375494, 00172375531, 00172375675, 00172375695, 00555198414,
00555198514, 10518010207, 10518010208, 10518010209, 51079096101,
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Hydoxyurea, Hydrea, Droxia-

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Ifosfamide/Ifex/Mesnex Kit-

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Figure 1.
CONSORT diagram

Figure 2.
Actual Survival by Treatment Type

Figure 3.
Predicted Survival by Treatment Type

Table 1

Sample means by treatment status before and after weighting by propensity score

	Prior to weighting by propensity score					After weighting by propensity score				
	Chemotherapy N= 1171	Chemotherapy and Surgery N= 265	Hospice N= 199	No treatment N= 403	p value	Chemotherapy N= 1171	Chemotherapy and Surgery N= 265	Hospice N= 199	No treatment N= 403	p value
Age 65–69	29.4	40.8	17.1	30.5	<0.001	29.9	31.2	25.0	30.9	0.61
Age 70–74	30.0	31.3	18.6	26.8	0.002	28.1	29.3	28.8	27.7	0.98
Age 75–79	27.2	20.0	29.6	25.1	0.04	26.2	24.6	28.3	25.3	0.89
Age 80-up	13.5	7.9	34.7	17.6	<0.001	15.8	14.8	18.0	16.1	0.86
White	91.9	92.1	93.5	87.8	0.08	91.0	90.1	93.2	90.8	0.80
Black	5.0 *	4.2	<5.5 *	5.7	0.37	5.0 *	6.2	<5.5 *	4.3	0.85
Other minority	5.0	3.8	<5.5 *	6.5	0.005	4.6	3.7	<5.5 *	4.9	0.80
Elixhauser comorbidity score	5.4	4.2	6.5	5.9	<0.001	5.5	5.8	5.6	5.6	0.97
Charlson comorbidity score	0.5	0.4	0.6	0.5	0.06	0.5	0.6	0.5	0.5	0.73
Charlson score 0	68.2	73.2	59.3	64.8	0.009	67.8	65.3	63.8	65.8	0.73
Charlson score 1	21.9	19.2	28.6	23.6	0.11	22.0	21.4	25.4	23.2	0.80
Charlson score 2+	9.9	7.5	12.1	11.7	0.24	10.2	13.3	10.8	11.0	0.83
Stage 3	71.5	78.5	70.9	76.7	0.03	73.4	72.9	71.0	74.1	0.94
Stage 4	28.5	21.5	29.1	23.3	0.03	26.6	27.1	29.0	25.9	0.94
Serous adenocarcinoma	85.4	81.9	85.4	80.1	0.08	83.7	82.9	84.3	82.8	0.97
Grade 1 or 2	17.4	16.6	23.1	18.6	0.30	18.1	19.1	17.9	18.1	0.99
Grade 3 or 4	67.0	69.8	58.8	68.0	0.08	67.0	65.2	67.5	67.1	0.97
Grade unknown	15.5	13.6	18.1	13.4	0.41	14.8	15.7	14.6	14.8	0.99
Northeast	20.9	17.7	12.6	22.8	0.004	20.1	16.9	15.2	20.0	0.40
South	15.4	12.5	18.6	15.1	0.34	15.4	15.2	17.4	15.9	0.94
Midwest	17.0	15.5	26.1	10.9	<0.001	16.5	17.6	17.9	16.8	0.96
West	46.3	52.8	42.2	50.9	0.05	47.6	48.5	47.6	47.3	1.00
Urban	54.1	56.2	44.7	59.3	0.008	54.3	55.3	55.9	53.4	0.96
Suburban	36.1	34.7	40.7	34.5	0.49	36.3	35.5	35.6	36.0	1.00
Rural	9.8	9.1	14.6	6.2	0.01	9.4	9.2	8.5	10.6	0.91

* Cell size < 11

Table 2

Factors associated with type of secondary treatment for patients with ovarian cancer

	Chemotherapy and surgery N=265	Hospice N=199	No Treatment N=403
Stage 3	reference	reference	reference
Stage 4	0.69 (0.53,0.90)	1.10 (0.77,1.59)	0.77 (0.63,0.93)
Serous adenocarcinoma	0.82 (0.55,1.23)	1.00 (0.57,1.76)	0.66 (0.52,0.83)
Other histology	reference	reference	reference
Elixhauser comorbidity score	0.98 (0.96,0.99)	1.02 (0.98,1.05)	1.01 (0.99,1.02)
Charlson comorbidity score	0.96 (0.86,1.07)	1.07 (0.88,1.29)	1.03 (0.88,1.21)
Grade 1 or 2	reference	reference	reference
Grade 3 or 4	1.16 (0.96,1.41)	0.65 (0.53,0.79)	0.85 (0.68,1.07)
Grade unknown	1.01 (0.59,1.73)	0.85 (0.52,1.39)	0.79 (0.64,0.97)
Age 65–69	reference	reference	reference
Age 70–74	0.74 (0.60,0.90)	1.03 (0.70,1.52)	0.89 (0.63,1.24)
Age 75–79	0.56 (0.36,0.85)	1.84 (1.08,3.15)	0.92 (0.70,1.22)
Age 80 up	0.43 (0.30,0.60)	4.45 (2.67,7.41)	1.24 (0.77,2.01)
Zip code median income (Census 2000)	1.01 (0.93,1.10)	0.97 (0.89,1.06)	1.00 (0.96,1.05)
Urban	reference	reference	reference
Suburban	0.94 (0.75,1.19)	1.34 (1.00,1.79)	0.86 (0.73,1.01)
Rural	0.98 (0.61,1.57)	1.58 (1.05,2.39)	0.70 (0.50,0.97)
Northeast	reference	reference	reference
South	0.83 (0.57,1.21)	1.90 (1.56,2.32)	1.02 (0.76,1.37)
Midwest	0.96 (0.67,1.37)	2.35 (2.06,2.68)	0.76 (0.69,0.84)
West	1.16 (0.88,1.51)	1.63 (1.29,2.07)	1.06 (0.94,1.19)
White	reference	reference	reference
Black	1.27 (0.74,2.18)	1.26 (0.65,2.46)	1.64 (0.99,2.72)
Other minority	0.74 (0.52,1.03)	0.38 (0.17,0.83)	1.55 (1.10,2.17)
Diagnoses year 1997	reference	reference	reference
Diagnoses year 1998	1.16 (0.54,2.50)	1.19 (0.55,2.58)	1.64 (0.99,2.71)
Diagnoses year 1999	0.56 (0.35,0.89)	0.63 (0.13,3.04)	1.66 (0.65,4.29)
Diagnoses year 2000	0.69 (0.29,1.67)	0.87 (0.41,1.84)	1.52 (0.53,4.33)
Diagnoses year 2001	0.90 (0.48,1.67)	1.17 (0.51,2.68)	1.53 (0.78,3.01)
Diagnoses year 2002	0.93 (0.48,1.81)	1.05 (0.49,2.23)	1.68 (0.83,3.40)
Diagnoses year 2003	0.92 (0.48,1.76)	0.70 (0.31,1.58)	1.82 (0.85,3.92)
Diagnoses year 2004	0.98 (0.52,1.85)	0.75 (0.41,1.38)	2.53 (1.20,5.34)
Diagnoses year 2005	0.61 (0.26,1.46)	0.96 (0.37,2.49)	3.08 (1.49,6.39)
Diagnoses year 2006	0.51 (0.20,1.28)	1.30 (0.45,3.78)	4.78 (2.38,9.60)
Diagnoses year 2007	0.44 (0.19,0.98)	0.43 (0.13,1.44)	10.13 (4.89,20.95)

Reference group: Chemotherapy only (N=1171)

Table 3

Factors Associated with Survival

	Log-Logistic Model HR (95%CI)	FMM True Non- Recurrence HR (95%CI)	FMM Untreated Recurrence HR (95%CI)	p-value of Difference
Chemotherapy only	reference	reference	reference	0.253
Chemotherapy & surgery	1.33 (1.20,1.46)	1.24 (1.05,1.46)	1.67 (1.13,2.47)	
Hospice	0.55 (0.51,0.59)	0.54 (0.49,0.60)	0.54 (0.36,0.79)	0.952
No Treatment	2.33 (1.97,2.75)	3.91 (2.88,5.31)	0.57 (0.42,0.78)	0.000
Age 65–69	reference	reference	reference	
Age 70–74	0.91 (0.82,1.00)	1.01 (0.90,1.13)	0.62 (0.40,0.96)	
Age 75–79	0.83 (0.71,0.95)	0.91 (0.82,1.01)	0.70 (0.62,0.80)	
Age 80+	0.80 (0.68,0.94)	0.85 (0.69,1.03)	0.94 (0.38,2.36)	
White	reference	reference	reference	
Black	0.87 (0.75,1.02)	0.95 (0.79,1.15)	0.66 (0.46,0.93)	
Other minority	0.93 (0.83,1.05)	1.00 (0.85,1.18)	0.89 (0.52,1.52)	
Stage 3	reference	reference	reference	
Stage 4	0.98 (0.91,1.05)	0.96 (0.86,1.07)	1.12 (0.89,1.42)	
Serous adenocarcinoma	0.88 (0.81,0.95)	0.84 (0.73,0.97)	1.19 (0.80,1.77)	
Other histology	reference	reference	reference	
Elixhauser comorbidity score	0.99 (0.99,1.00)	1.00 (0.99,1.00)	1.00 (0.99,1.02)	
Charlson comorbidity score	0.91 (0.87,0.96)	0.91 (0.85,0.97)	1.04 (0.81,1.33)	
Grade 1 or 2	reference	reference	reference	
Grade 3 or 4	1.06 (0.96,1.17)	1.00 (0.92,1.09)	1.32 (0.92,1.89)	
Grade unknown	0.99 (0.90,1.10)	1.08 (0.94,1.24)	0.73 (0.50,1.05)	
Zip code median income (Census 2000)	1.00 (0.98,1.02)	0.99 (0.97,1.02)	1.04 (1.00,1.08)	
Urban	reference	reference	reference	
Suburban	0.93 (0.80,1.10)	0.91 (0.80,1.03)	1.07 (0.62,1.83)	
Rural	0.86 (0.74,1.00)	0.85 (0.74,0.97)	1.24 (0.82,1.89)	
Northeast	reference	reference	reference	
South	1.01 (0.94,1.09)	1.05 (0.89,1.23)	1.12 (0.75,1.68)	
Midwest	0.95 (0.87,1.04)	1.04 (0.94,1.14)	0.95 (0.74,1.22)	
West	1.07 (0.96,1.19)	1.18 (1.04,1.35)	0.76 (0.44,1.34)	
Diagnoses year 1997	reference	reference	reference	
1998	0.90 (0.74,1.11)	0.88 (0.75,1.03)	1.37 (0.91,2.07)	
1999	0.93 (0.78,1.11)	0.99 (0.79,1.23)	1.66 (0.88,3.15)	
2000	0.94 (0.76,1.16)	1.07 (0.91,1.26)	1.21 (0.90,1.62)	
2001	0.95 (0.85,1.05)	0.97 (0.83,1.13)	1.76 (1.22,2.54)	
2002	0.93 (0.84,1.02)	0.85 (0.71,1.02)	2.22 (1.76,2.80)	
2003	0.98 (0.88,1.09)	0.94 (0.84,1.07)	2.48 (1.61,3.83)	
2004	1.02 (0.82,1.27)	1.20 (0.95,1.51)	1.27 (0.94,1.72)	
2005	0.91 (0.74,1.12)	0.97 (0.78,1.22)	1.37 (1.13,1.67)	

	Log-Logistic Model HR (95%CI)	FMM True Non- Recurrence HR (95%CI)	FMM Untreated Recurrence HR (95%CI)	p-value of Difference
2006	0.92 (0.78,1.08)	0.94 (0.80,1.12)	1.30 (0.81,2.08)	
2007	0.84 (0.72,0.98)	0.78 (0.64,0.95)	2.16 (0.74,6.26)	
Class probability		0.77 (0.68,0.85)	0.23 (0.15,0.32)	

FMM: Finite Mixture Model