HHS Public Access

Author manuscript

*Gynecol Oncol*. Author manuscript; available in PMC 2015 August 06.

Published in final edited form as:

*Gynecol Oncol*. 2013 August ; 130(2): 295–299. doi:10.1016/j.ygyno.2013.04.055.

# Recurrence patterns after extended treatment with bevacizumab for ovarian, fallopian tube, and primary peritoneal cancers

**Minh D. Dao**, **Laura M. Alwan**, **Heidi J. Gray**, **Hisham K. Tamimi**, **Barbara A. Goff**, and **John B. Liao***

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Washington, Seattle, Washington, USA

## Abstract

**Objective—**To evaluate patterns of recurrence for ovarian, fallopian tube, and primary peritoneal cancer patients undergoing extended treatment with bevacizumab (BEV).

**Methods—**A retrospective review of patients with primary ovarian, fallopian tube, or peritoneal cancer treated with BEV alone or in combination with other chemotherapy from 2001 to 2011 was performed. Qualified patients were identified by chemotherapy records. Electronic medical records, labs, and imaging reports were reviewed and abstracted.

**Results—**Of 108 patients identified, 89 patients met study criteria by having disease progression either during treatment with BEV or after discontinuing BEV without initiating any other treatment. Patients on extended BEV therapy (> 12 cycles) were more likely to recur in extra-visceral sites ($p = 0.04$), especially in lymph nodes ($p = 0.0002$), and presented with fewer symptoms at time of recurrence ($p = 0.02$), compared to patients who had received ≤ 12 cycles. CA-125 becomes less reliable for the detection of recurrent disease with extended BEV therapy ($p = 0.03$ for ≤ 12 cycles vs. $p = 0.08$ for >12 cycles). Radiology was superior to CA-125, symptom, and physical exam, in detecting recurrence with extended BEV therapy (all $p < 0.0001$).

**Conclusions—**Extended treatment with BEV in ovarian, fallopian tube, and peritoneal cancers results in alterations in the patterns of recurrence. Radiologic imaging is more reliable than CA-125, symptoms, or physical exam, in identifying recurrent disease in patients undergoing BEV treatment. As novel targeted therapies continue to be employed, guidelines for gynecologic cancer surveillance must continue to be reexamined.

*Corresponding author: John B. Liao, MD, PhD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Washington, Box 356460, 1959 NE Pacific Street, Seattle, WA 98195-6460, USA. Phone: 1+ (206) 543-3669. Fax: 1 + (206) 543-3915. johnliao@u.washington.edu.

Presented in part at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer, Los Angeles, California, USA. March 9 – 12, 2013.

**Conflict of Interest Statement**: The authors declare no conflicts of interest.

## Introduction

Mortality rates for ovarian cancer have improved only modestly over the recent decades. Since the majority of patients with advanced ovarian cancer will recur in the first 2 – 3 years following clinical response, finding agents that will delay or alter recurrence is a priority. Molecular targeted therapies with novel mechanisms of action are being applied to achieve this goal. Bevacizumab (BEV), a monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A), is one such agent [1-3]. However, because its mechanism of action, anti-angiogenesis, differs significantly from traditional cytotoxic chemotherapies, how disease recurs in patients treated with BEV may also differ.

Approximately 26-50% of ovarian cancers recur in the pelvis [4, 5]. Other common sites of recurrence include retroperitoneal lymph nodes, upper abdomen, and lungs [6, 7]. Rare sites of recurrence include the brain or presentation as cutaneous lesions [8]. Recently, a study by Tanner et al. reported that ovarian cancer patients treated with intravenous chemotherapy tend to recur intra-abdominally (38.6% versus 13.3%, $p = 0.006$), while those undergoing intra-peritoneal chemotherapy are more likely to recur outside the abdominal cavity (45.5% versus 23.3%, $p = 0.018$) [9].

We sought to understand how ovarian, fallopian tube, and primary peritoneal cancer patients receiving BEV treatment recur and the effectiveness of methods used to detect recurrences. We hypothesized that patients undergoing extended BEV therapy could have altered patterns of recurrence and symptoms of recurrence due to its novel mechanism of action. A better understanding of recurrence patterns in patients receiving BEV may help in evaluating the effectiveness of current cancer surveillance practices in this population.

## Patients and Methods

We conducted a retrospective review of data from ovarian, fallopian tube, and primary peritoneal cancer patients who were treated with BEV alone or in combination with other cytotoxic agents by the Division of Gynecologic Oncology at the University of Washington and the Seattle Cancer Care Alliance from January 1, 2001 to December 31, 2011. The study was approved by the Cancer Consortium Institutional Review Board at the University of Washington. Qualified patients were identified by chemotherapy records and their medical charts were reviewed. Patients received BEV either at initial adjuvant chemotherapy or at subsequent disease relapses. Patients were excluded if their medical records were incomplete or if they had not recurred by the date of chart review.

### Criteria to determine disease recurrence during or after BEV treatment

Clinical records were reviewed to abstract: age, ethnic background, stage, histology, surgical outcome, node status, chemotherapy agents used in neoadjuvant, adjuvant, and recurrent disease treatment, and total number of BEV cycles given. Patients received various BEV regimens (Table 1), with dosages of 2.5 mg/kg/week ($n = 9$) or 5 mg/kg/week ($n = 80$) [1-3, 10]. Recurrent disease information abstracted included serum CA-125 immediately prior to starting BEV therapy and at recurrence, radiologic evidence of recurrence, physical exams, patient report of symptoms, site(s) of recurrence, and size of recurrent lesions. Recurrences

in many patients were detected by single or multiple methods (radiologic imaging, CA-125, symptoms, or physical exams). All patients had radiologic studies and CA-125 obtained at least every 3 cycles of chemotherapy or as otherwise indicated for patients participating in clinical studies. The patients' symptoms were recorded based on clinical notes at surveillance visits. Patients might have no symptoms (well-being), single, or multiple symptoms at recurrence. Recurrent disease was categorized into specific site/organs and subsequently grouped into patterns (extra-abdominal versus intra-abdominal, abdominal versus nodal versus distant) based on a published study by Tanner et al [9]. Although patients were individually determined to have recurrence by their attending physicians, we were able to categorize the providers' criteria into one or more of the following: 1) new onset of persistent symptom(s) different from their baselines during treatment 2) physical exam (pelvic, abdominal, lymph node palpation) documenting new growth of lesions 3) change in serum CA-125 from baseline 4) radiologic evidence of new growth or increased in size of previously noted lesions based on RECIST criteria. The attending physicians' recurrence assessments were consistent with criteria suggested in published studies and guidelines [4-7, 11-14]. We therefore adopted these criteria in defining recurrences in our study. The majority of patients recurred while receiving BEV. The remaining patients received BEV before discontinuing all therapies due to personal request or physicians' recommendations (due to BEV toxicities or other reasons). They were observed until recurrence.

### Statistical analysis

Discreet variables were analyzed using Fisher exact test and Chi-squared test. Continuous variables were compared using Mann Whitney test. All statistical tests were two tailed with $p < 0.05$ considered significant. All statistical analyses were performed on GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com).

## Results

### Clinical characteristics of study population

108 patients were identified and 89 were included in the study. Nineteen patients were excluded because they had not recurred at the date of chart review (n = 12), had incomplete medical records (n = 5), or did not receive BEV during their participations in the clinical trials after group assignment was disclosed at recurrence (n = 2). Approximately 79% of patients (n = 70) were on active treatment with BEV at time of recurrence. The remaining patients (n = 19) were treated with BEV and then discontinued all therapies until disease progression. The reasons for BEV discontinuation included physician recommendations (n = 7), BEV toxicities (n = 8), and patient request (n = 4). Twenty-eight patients (31%) experienced BEV toxicities during their treatments, including hypertension and/or proteinuria alone (n = 20), hypertension with severe headache (n = 3), hypertension with gastrointestinal bleed (n = 1), hypertension with nosebleed (n = 1), nosebleed and gastrointestinal bleed (n = 1), nosebleed and headache (n = 1), and bowel perforation (n = 1). Although some patients experienced BEV toxicities, twenty patients remained on BEV treatment while their toxicities (mostly hypertension) were medically treated or after BEV

dosage reduction. The median number of total BEV cycles received for the whole group was 12 (range 2 – 51 cycles). This is similar to study patients in the OCEANS trial [3]. We therefore divided the patients into 2 groups, those receiving ≤ 12 cycles (median 5 cycles, n = 47) and those receiving > 12 cycles (median 19.5 cycles, n = 42), and further compared their recurrence patterns and symptoms.

## Comparison of general baselines between two groups

The two BEV groups had very similar baseline characteristics (Table 1). The majority of patients in both groups had stage III/IV disease and serous histology. Optimal cytoreduction at primary surgery was achieved in 64% of patients in the ≤ 12 cycles group and 55% of those in the > 12 groups (p = 0.52). Original operative reports or radiologic reports at time of primary cytoreductive surgeries were not available for all our study patients (approximately 20% of the patients transferred their postoperative/follow-up care to our institutions). Determining the number of patients with initial intra-abdominal and/or sub-diaphragmatic tumor burden for each group was not possible. However, of patients whose primary operative reports were available, we cautiously inferred that the initial intra-abdominal and/or sub-diaphragmatic tumor burden was similar in both groups by the absence of statistical significance between the number of patients having optimal and suboptimal surgical outcome between the two groups (Table 1). At least 90% of BEV treatments were for patients with recurrent disease (first recurrence n = 28, second recurrence n = 14, third recurrence and beyond n = 39) in both groups. The median serum CA-125 level prior to starting BEV therapy was 80 units/mL (range 5 – 2458 units/mL) for the ≤ 12 cycles group and 35 units/mL (range 3 – 4607 units/mL) for the > 12 cycles group, though this difference was not statistically significant (p = 0.92). There was no difference in the number of chemotherapy regimens received prior to BEV therapy between both groups (median 1 prior regimen (range 0 – 8) for ≤ 12 cycles group versus median 2 prior regimens (range 0 – 6) for > 12 cycles group, p = 0.82). Secondary cytoreductive surgeries prior to BEV therapy were performed in equivalent number of the patients in both groups. Table 1 also lists the chemotherapy regimens that were used in combination with BEV for each group. Ten percent of patients received BEV at dosage of 2.5 mg/kg/week and the remaining 90% were dosed at 5 mg/kg/week.

## Symptoms and sites of recurrence

In all 89 patients who recurred after BEV treatment, the most commonly reported symptoms of recurrence were abdominal pain/bloating (42.7%) and ascites (29.2%), while the most frequent recurrent sites were abdominal lymph node (56.2%), liver (50.6%), and lung (43.8%). Three patients (3%) had bowel obstruction during BEV treatment, but only one patient (1%) had bowel perforation. There were 5 patients with brain metastases, 3 patients with skin metastases, and 2 patients with bone metastases. Almost one-third of the patients had no symptoms at time of recurrences. No patients were noted to complain of urinary symptoms as sign of recurrence, which were common in pre-treatment patients with ovarian malignancy [15]. When patients were compared according to the extent of their BEV therapy duration, there were no differences in terms of the maximal size of recurrent lesions (median 2.2 cm versus 2.7 cm, p = 0.24) or the number of recurrent sites (median of 3 sites for each group, p = 0.61). However, patients treated with > 12 cycles of BEV complained of

significantly fewer symptoms at recurrence (p = 0.02) than those treated with ≤ 12 cycles (Table 2).

We further evaluated the two groups according to specific symptoms and sites of recurrence. We observed that extended BEV therapy resulted in a higher probability of recurrence in extra-visceral sites (nodes, lung, brain, skin, and bone metastases, p = 0.04) than visceral compartments (pelvis, vaginal cuff, liver, diaphragm, spleen, and peritoneal metastases), compared patients on shorter BEV therapy. The proportions of patients recurring in abdominal or extra-abdominal lymph nodes, lung, liver, and brain/skin/bone, were not statistically different between two groups (table 3). Interestingly, patients who received fewer BEV cycles were more likely to recur in the vaginal cuff (19% vs. 2%, p = 0.01) and in the bowel (30% vs. 12%, p = 0.04). In contrast, patients on longer BEV therapy tended to be asymptomatic at time of their recurrences (18% vs. 9%, p = 0.03). When patients had symptoms at the time of recurrence, abdominal pain/bloating (p = 0.02) and nausea/vomiting (p = 0.004) were significantly associated with those on shorter BEV therapy. The presence of ascites, which was common in both groups, was not significantly influenced by the extent of BEV cycles (19% vs. 10%, p = 0.16). Bevacizumab has previously been reported to be effective in reducing symptomatic ascites in patients with refractory ovarian cancer [16]. The proportion of patients reporting tiredness/fatigue, dyspnea, or neurological symptoms (unusual headache, new onset of seizure, abrupt vision change, gait disturbance) was not statistically different between the two groups (Table 3).

## Patterns of recurrence

Based on the work by Tanner and colleagues [9], we categorized recurrence sites into three general patterns: intra-abdominal (lesions in lower and upper abdomen, including liver, spleen, and diaphragm), nodal (any abdominal or extra-abdominal lymph nodes), and distant (any extra-abdominal metastasis - lung, brain, skin, bone). We found 32 patients had intraabdominal visceral recurrences alone and 57 patients had extra-abdominal recurrences alone or both intra- and extra-abdominal recurrences. Median number of total BEV cycles was 12 for both groups (range 3 - 51 cycles for intra-abdominal group and 2 – 48 cycles for extra-abdominal/both group, p = 0.74). We concluded that intra-abdominal visceral recurrences alone (which might give rise to earlier symptoms and/or be detected earlier by examinations and radiologic imaging) were unlikely the significant factor that limited the number of BEV cycles in our study. When comparing the ≤ 12 BEV cycles group and the > 12 BEV cycle group, no difference was observed within intra-abdominal recurrence (p = 0.67), nodal metastasis (p = 0.25), and distant metastasis (p = 0.25). When the nodal and distant recurrences were compared with intra-abdominal recurrences for each BEV group, a distinctive pattern of recurrence was observed in those receiving extended BEV therapy. Specifically, a significant number of patients in the > 12 BEV cycles had nodal recurrences relative to intra-abdominal lesions (78.6% versus 38.1%, p = 0.0002). No statistical difference was observed for patients with distant recurrences (54.8% versus 38.1%, p = 0.19). In the ≤ 12 BEV cycles group, the proportions of patients with nodal and distant recurrences were not statistically different from that of intra-abdominal recurrence (p = 0.09 for nodal metastasis and p = 1.0 for distant metastasis).

### Methods to detect recurrence

We studied the effectiveness of methods (radiology, serum CA-125, symptom, physical exam) used to detect recurrences in patients receiving BEV. Elevation of CA-125 becomes less reliable for the detection of recurrent disease with extended BEV therapy. In patients on shorter BEV therapy (≤ 12 cycles), CA-125 level was higher at recurrence than that at pre-BEV treatment (mean 655 units/mL versus 307 units/mL, p = 0.03). In contrast, CA-125 level was not predictive of recurrence for those patients on extended BEV therapy (>12 cycles) (mean 327 units/mL versus 289 units/mL, p = 0.08). Regardless of when BEV was initiated (i.e., after primary cytoreductive surgery or after first recurrence), serum CA-125 at recurrence during BEV therapy was not predictive for metastasis (distant vs. intra-abdominal, p = 0.19) or number of metastatic sites (1-3 sites versus ≥ 4 sites, p = 0.36). In our 89 study patients, 97% had CT, while 1% had US, 6% had MRI, and 13% had PET concurrent with CT to detect recurrence. Physical exams were performed for 86 patients (97%) at time of recurrence. There were 77 patients (87%) whose first recurrences were detected by a radiologic modality, 47 patients (53%) by CA-125, 45 patients (51%) by symptoms, and only 8 patients (9%) by physical exam. Twenty-six percent of the 89 patients had first evidence of recurrence detected by one method, 47% by two methods, and 27% by three methods. Use of serum CA-125 and reported symptoms were equally effective at detecting recurrence in both groups. Of patients receiving shorter BEV therapy, radiology (by one or combined imaging modalities) was more effective in detecting recurrence than serum CA-125 (p = 0.01), symptoms (p = 0.01), or physical exam (p < 0.0001). The superiority was even more noticeable in those receiving extended BEV treatment, with odd ratios (range 13 – 260) favoring radiology over the other three methods (Table 4). Overall, CA125 became less effective in detecting recurrence after patients received BEV therapy alone or in combination with other regimens, especially for those getting more than 12 cycles of BEV, while physical exam remained the least effective method in detecting recurrence in either group.

## Discussion

Recent clinical trials have reported that ovarian cancer patients treated with BEV as part of their first line of treatment had longer progression-free survival compared to patients treated with traditional cytotoxic therapies [1, 2]. Bevacizumab may selectively alter tumor biology and metastasis pathways that are not observed in patients treated with traditional cytotoxic therapy. Specifically, patients treated with BEV might have different profiles of recurrent clinical symptoms and patterns of disease recurrence compared to those who receive traditional intravenous / intraperitoneal cytotoxic chemotherapies [9]. Our study suggests that patients who received more than 12 cycles of BEV present with fewer symptoms at time of recurrence compared to those receiving 12 cycles or less. Patients on extended BEV therapy also predominantly recurred in lymph nodes. Regardless of when BEV was started, radiology was superior to CA-125, patient symptoms, and physical exams, in detecting recurrent disease during the therapy.

Ovarian cancer recurrence usually presents in the abdomen as a result of peritoneal or lymphatic spread, and rarely from hematogenous dissemination. Lymphatic metastasis at

time of primary surgical treatment has been estimated to be 30 – 70% for stages III/IV [17-19]. We observed that lymph nodes (especially extra-abdominal ones) were the most common site of recurrence, particularly after prolonged BEV treatment. A recent retrospective analysis reported similar patterns of recurrence [9]. In that study, ovarian cancer patients treated with traditional intravenous cytotoxic regimens tended to recur in the lower abdomen and pelvis, while those treated with intra-peritoneal therapy were more likely to recur at extra-abdominal sites, specifically in extra-abdominal lymph nodes. The incidence of brain metastasis associated with BEV therapy also appears higher in our study (5.6%) than the less than 2% incidence previously reported [18, 20, 21]. The higher incidences of central nervous system and lymphatic metastasis seen in our study could be due to the inability of our study size to properly assess these rare occurrences. In addition, a number of patients were treated with several chemotherapeutic regimens prior to receiving BEV, thus the incidence of extra-abdominal metastasis may be higher as the disease reaches its terminal course. However, it is difficult to attribute the BEV therapy itself or the prolonged duration of the disease as the primary cause of increased metastasis to the central nervous system and lymph nodes, because extra-abdominal disease is infrequent at time of first recurrence.

Twenty-seven percent of patients (n = 24) in our study received BEV as part of clinical trials. We acknowledge that requirements for patients to enroll in specific trials may introduce selection bias in a retrospective study. In addition, radiologic studies performed on patients in clinical trials may be more frequent than on those treated outside of study protocol. This increased frequency may detect recurrence earlier and possibly makes radiologic imaging statistically superior to other methods. In some studies, the false-positive rate of CA-125 in detecting recurrence is less than 2%, while that of CT scan is 14% [22, 23]. In contrast, a meta-analysis of 34 studies reports that the pooled sensitivity and specificity of CA-125 are 69% and 93%, of CT are79% and 84%, and of PET-CT are 91% and 88%, respectively [24]. Previous studies show that ovarian cancer patients treated with traditional cytotoxic therapy had their CA-125 increase preceding clinical progression by 3 – 5 months [13, 23, 25]. Clearly, the optimal strategy for the detection of recurrent ovarian cancer remains elusive.

Our study with patients treated with BEV therapy suggests that CA-125 is not a reliable marker to identify recurrent disease in this population, especially for those patients on extended treatment. Bevacizumab inhibits tumor growth by inhibiting angiogenesis, which may modulate CA-125 production and secretion and may affect its reliability as a tumor marker. The change in CA-125 based on published criteria only detected recurrence in approximately 50% of our patients, while radiologic imaging discovered recurrence in 85% of these patients concurrently. A number of studies have shown that CA125 changes may be seen in the setting of stable disease [26, 27]. Limitations regarding the use of CA125 levels to follow disease during treatment with bevacizumab have also recently been reported. Our findings regarding the limitations of CA-125 are consistent with a prior study of 15 recurrent ovarian cancer patients treated with sorafenib and bevacizumab, in which the authors reported that CA-125 changes did not agree with objective imaging (67% concordance) in predicting disease behavior [28]. In retrospective analysis of 62 patients with persistent or recurrent ovarian or peritoneal cancer treated with bevacizumab (Gynecologic Oncology

Group protocol 170-D), Randall and colleagues observed that CA-125 and RECIST-defined progression correlated in most cases (31% and 21%, respectively), but 12.9% of those with CA-125 defined progression remained progression-free according to RECIST criteria for at least 5.7 months [29]. These findings further support our conclusion that radiologic imaging may be more reliable than CA-125 to detect disease progression in patients treated with BEV. These studies and our own are consistent with a prospective randomized study of relapsed ovarian cancer patients, in which the authors conclude that routine CA-125 measurement is less effective for disease surveillance [30].

Extended treatment with BEV in ovarian, fallopian tube, and peritoneal cancers leads to alterations in the patterns of recurrence. Radiologic imaging emerges as the best surveillance modality for patients treated with BEV. This is most evident in those women receiving more than 12 cycles of BEV, because their recurrences are more likely to be asymptomatic or they may present with fewer symptoms. The Society of Gynecologic Oncologists, in agreement with the National Comprehensive Cancer Network, published guidelines regarding ovarian cancer surveillance [7]. Review of symptoms and physical examination are recommended every three months for two years and then every six months for years 3 – 5, and annually thereafter. CA-125 monitoring and radiologic imaging are considered optional unless recurrence is suspected. This surveillance strategy could miss a significant number of recurrences for patients treated with BEV. In addition, it could potentially lead to early and unnecessary discontinuation of BEV if relying only on CA-125 monitoring. CA-125 criteria were formulated exclusively from cytotoxic therapy and these criteria may not be as reliable in the setting of agents with novel mechanisms of action. As targeted biological therapies are increasingly used to treat ovarian cancer patients, the guidelines for ovarian cancer surveillance need to be re-examined continually to reflect our new understanding of the disease and its treatments.

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## Highlights

- Ovarian cancer patients treated with bevacizumab predominantly recurred in lymph nodes.
- Patients on extended bevacizumab treatment presented with fewer symptoms at time of recurrence than those receiving fewer cycles of bevacizumab.
- Radiologic imaging is superior to serum CA-125, symptoms, and physical exam for the detection of recurrent disease in patients treated with bevacizumab.

## Table 1

### General characteristics

| Characteristic | No. of patients (%) | | p – value[a] |
|---|---|---|---|
| | ≤12 BEV cycles N = 47 | >12 BEV cycles N = 42 | |
| *Age at surgery (median)* | 57 | 52.5 | 0.06 |
| *Ethnicity* | | | 0.58 |
| Caucasian | 40 (85) | 33 (79) | |
| Others/not recorded | 7 (15) | 9 (21) | |
| *FIGO Stage* | | | 0.26 |
| I/II | 4 (9) | 1 (2) | |
| III/IV | 42 (89) | 38 (91) | |
| Unknown/Not stage | 1 (2) | 3 (7) | |
| *Histology* | | | 0.33 |
| Serous | 33 (70) | 34 (81) | |
| Others/unknown | 14 (30) | 8 (19) | |
| *Surgical outcome* | | | 0.52 |
| Optimal cytoreduction | 30 (64) | 23 (55) | |
| Sub-optimal cytoreduction | 6 (13) | 9 (21) | |
| Unable to determine[b] | 11 (23) | 10 (24) | |
| *Node status* | | | 0.69 |
| Positive | 22 (47) | 16 (38) | |
| Negative | 9 (19) | 10 (24) | |
| Unknown/not sent | 16 (34) | 16 (38) | |
| *Neoadjuvant therapy* | | | 0.08 |
| Paclitaxel/docetaxel + carboplatin | 10 (21) | 3 (7) | |
| No neoadjuvant treatment | 37 (79) | 39 (93) | |
| *BEV use in* | | | 1.0 |
| Primary disease | 4 (9) | 4 (10) | |
| Recurrent disease | 43 (91) | 38 (90) | |
| *Secondary cytoreduction prior to BEV* | | | 1.0 |
| Performed[c] | 13 (26) | 11 (26) | |
| Not performed | 30 (62) | 26 (62) | |
| *BEV use in combination with* | | | |
| ± Paclitaxel/docetaxel ± carboplatin/cisplatin | 6 (13) | 14 (33) | |
| Topotecan | 27 (57) | 13 (31) | |
| Gemcitabine + carboplatin | 5 (11) | 5 (12) | |
| Liposomal doxorubicin | 3 (6) | 1 (2) | |
| Gemcitabine | 1 (2) | 3 (7) | |
| Cyclophosphamide | 0 (0) | 2 (5) | |
| No chemotherapy | 5 (11) | 4 (10) | |

[a] Comparison was performed using Mann Whitney test, Fisher exact test, or Chi-squared test, as appropriate.

[b] Operative notes unavailable

[c] One patient in the ≤ 12 group had secondary cytoreductive surgery after BEV therapy

## Table 2
### Overall effects of BEV therapy duration

| Effect | Median (mean) | | p – value[a] |
|---|---|---|---|
| | ≤ 12 cycles N = 47 | > 12 cycles N = 42 | |
| Largest size of recurrent lesion (in cm)[b] | 2.2 (3.0) | 2.7 (3.7) | 0.24 |
| No. of recurrent sites[b] | 3 (3.4) | 3 (3.6) | 0.61 |
| No. of symptoms[c] | 2 (1.9) | 1 (1.2) | **0.02** |

[a] Effects were compared for patients treated with ≤ 12 cycles versus > 12 cycles, using Mann Whitney test. *p < 0.05 considered significant.*

[b] Sizes (range 0.3 – 15 cm) and sites (range 1 – 7) abstracted from radiologic (CT ± MRI ± PET ± US) reports.

[c] Symptoms (range 0 – 5) abstracted from clinical notes.

## Table 3
## Sites and symptoms of recurrence based on BEV therapy duration

| | No. of patients (%) | | |
|---|---|---|---|
| | ≤12 BEV cycles N = 47 | >12 BEV cycles N = 42 | p-value[a] |
| *Sites* | | | |
| Abdominal lymph nodes | 22 (47) | 28 (67) | 0.06 |
| Extra-abdominal lymph nodes | 18 (38) | 20 (48) | 0.55 |
| Lung | 19 (40) | 20 (48) | 0.70 |
| Liver | 22 (47) | 23 (55) | 0.45 |
| Brain/Skin/Bone | 4 (9) | 6 (14) | 0.39 |
| Vaginal cuff | 9 (19) | 1 (2) | **0.01** |
| Bowel | 14 (30) | 5 (12) | **0.04** |
| *Symptoms*[b] | | | |
| Well-being | 8 (17) | 16 (34) | **0.03** |
| Abdominal pain/bloating | 26 (55) | 12 (26) | **0.02** |
| Ascites | 17 (36) | 9 (19) | 0.16 |
| Nausea/vomiting | 15 (32) | 3 (6) | **0.004** |
| Tiredness/fatigue | 8 (17) | 8 (17) | 0.62 |
| Dyspnea | 6 (13) | 8 (17) | 1.0 |
| Neurological | 4 (9) | 5 (11) | 0.73 |

[a] Sites and symptoms were compared for patients treated with ≤ 12 cycles versus > 12 cycles, using Fisher exact test. *$p < 0.05$ considered significant*.

[b] Enlarged lymph node, back pain, and constipation were not included in the table due to insufficient number of patients in each group for statistical analysis.

## Table 4
### Methods detecting recurrent diseases during or after BEV therapy

| | Odds Ratio [95% Confidence Interval][b] | | | |
|---|---|---|---|---|
| **Method[a]** | **≤12 BEV cycles N = 47** | **p – value** | **>12 BEV cycles N = 42** | **p – value** |
| Radiology[c] | | | | |
| *vs* CA-125 | 3.4 [1.4 – 8.6] | **0.01** | 13 [3.5 – 49] | < **0.0001** |
| *vs* Symptom | 3.4 [1.4 – 8.6] | **0.01** | 16 [4.2 – 59] | < **0.0001** |
| *vs* Physical exam | 29 [9.4 – 89] | < **0.0001** | 260 [41 – 1642] | < **0.0001** |
| CA-125 | | | | |
| *vs* Symptom | 1.0 [0.4 – 2.3] | 1.0 | 1.2 [0.51 – 2.9] | 0.82 |
| *vs* Physical exam | 8.5 [3.0 – 24] | < **0.0001** | 20 [4.3 – 94] | < **0.0001** |
| Symptom | | | | |
| *vs* Physical exam | 8.5 [3.0 – 24] | < **0.0001** | 17 [3.5 – 77] | < **0.0001** |

[a] Recurrence may be first detected by one or multiple methods.

[b] Odds ratios were calculated for each listed method versus others. Methods of detection were compared using Fisher exact test. *$p < 0.05$ considered significant*.

[c] By one or combined imaging methods (±CT ± MRI ± PET ± US).