



# Intraperitoneal (IP) port cytology after completion of primary therapy for advanced stage ovarian cancer: A novel approach to a “second look”

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## HIGHLIGHTS

- Disease status after completion of primary therapy influences prognosis.
- Second look laparotomy is invasive and does not change outcomes.
- IP port cytology is an accurate surrogate for second look laparotomy.
- Positive cytology was associated with earlier recurrence and death.
- High risk patients can be stratified to clinical trials or consolidation therapy.

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## ABSTRACT

**Objective.** To determine whether IP port cytology predicts early recurrence and/or poor prognosis in patients with ovarian cancer who have completed primary therapy.

**Methods.** A prospective study of patients with advanced stage ovarian cancer undergoing IP port removal after debulking followed by IV/IP chemotherapy was performed. Ports were flushed with 10 cc of normal saline into ThinPrep fixative to be analyzed for cytology. Results were correlated with clinical factors and cancer outcomes. Survivals were calculated using Kaplan-Meier curves and compared using log-rank analysis.

**Results.** Effluent from 53 IP ports was analyzed, and patients were followed for a median of 62 months. Mean age was 58.5, with the majority of patients being white (90%), with stage 3 (62%), serous histology (87%). Seven (13.2%) patients had positive IP cytology. POS and NEG groups were similar with regard to age, BMI, stage, grade, and GOG status. Patients with POS results had increased risk of recurrence HR 3.2 (95%CI 0.4, 28.9), and death HR 6.5 (95%CI 0.7, 58.8), and were more likely to recur before 12 months, 71% vs. 22% ( $p = 0.007$ ). Compared to NEG, POS conferred a shorter median survival with PFS of 32 vs. 7 months ( $p = 0.02$ ) and OS of 84 vs. 42 months ( $p = 0.04$ ).

**Conclusions.** IP port cytology is predictive of recurrence and survival in patients with ovarian cancer. This inexpensive test may serve as an adjunct to imaging and tumor markers to determine disease status at the completion of treatment. Further study should investigate how this may impact management.

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## 1. Introduction

A diagnosis of ovarian cancer carries a grim prognosis. It has the highest fatality to case ratio of all gynecologic malignancies. More than two-thirds of patients have advanced stage disease at the time of diagnosis [1]. Although 75% of these patients will have a complete clinical response to therapy, 75% will recur within 2 years. The high recurrence rate in patients with a complete clinical response is almost certainly

due to the presence of unrecognized microscopic disease. A series of trials attempted to surgically evaluate ovarian cancer patients at the end of therapy with a second look laparotomy. Unfortunately, despite finding a significant percentage of patients with macroscopic and microscopic residual disease, earlier treatment demonstrated no benefit in survival compared to treatment upon clinical recurrence, and it was associated with more chemotherapy, more toxicity and decreased quality of life [2–4]. Along this conundrum, numerous studies evaluated if continued therapy after completion of primary therapy (consolidation or maintenance) could prolong survival in ovarian cancer patients. Although some studies demonstrated a modest improvement in progression free survival [5–7], all were associated with increased toxicities, lower quality of life, and no improvement in overall survival [8,9].

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Fig. 1. Example of port flush and cytology of effluent.

Intra-peritoneal (IP) chemotherapy is a delivery method strategy that has consistently shown improvements in survival. Three large GOG trials showed a significant increase in survival ranging from 8 to 17 months with the addition of an IP component to a traditional intravenous (IV) regimen [10–12]. The presence of an IP port offers a potential window into the abdomen after therapy is completed; a small prospective study found that IP port cytology is a sensitive and specific test for microscopic disease in patients undergoing second look laparotomy [13].

Our hypothesis is that intra-peritoneal port cytology is also predictive of early recurrence and survival in ovarian cancer patients with a complete clinical response to primary therapy.

## 2. Methods

This was a prospective cohort study approved by the IRB at the University of South Alabama. Eligible patients had advanced stage ovarian cancer and had a complete clinical response to primary therapy including surgery (either primary or interval debulking) plus taxane/platinum based chemotherapy with at least one completed IP cycle, depending on tolerability. All patients had their IP ports removed between 2007 and 2012 after completion of chemotherapy. Patients were excluded if they had evidence of persistent or progressive disease based on CT or CA-125 at the time of removal. After removal, each port was flushed with 10 cc of normal saline into ThinPrep® Cytology Fixative. This was sent for cytology and histology (Fig. 1).

A negative result was assigned if no malignant cells were found. Any report resulted as suspicious, atypical or abnormal was considered as a positive result. No change in therapy was made based upon results of aspiration. Progression free survival was calculated as months elapsed from completion of chemotherapy to the date of recurrence documented in the medical record. Overall survival was calculated as months elapsed from first tissue diagnosis to either the date of death or the date of last known follow-up. Patients were divided into 2 groups: Positive (POS) and Negative (NEG) IP fluid. Demographic, surgico-pathologic, and survival variables were evaluated and compared between the two groups. Chi-square and standard *t*-test were used to evaluate these variables and Kaplan-Meier curves with a log rank analysis were used to evaluate survival in months.

## 3. Results

### 3.1. Demographics

A total of 53 patients were included in the analysis. The majority of patients in both groups had grade 3 (83%), stage 3 (62%), papillary serous (87%) ovarian cancer at the time of diagnosis. The mean age was

58.5, and 48 (90%) were white. 43 patients (81%) had a performance status of 0, and only 1 patient had a performance status greater than 1. No statistically significant difference was found between the two groups in terms of age, BMI, race, and GOG performance status as well as stage, grade and histology. (Table 1) All patients had no evidence of disease after completion of chemotherapy, which was defined by a negative CT scan and a normal CA-125.

### 3.2. IP port results

46 (86.8%) patients had a NEG result on IP port flush, while 7 (13.2%) had a POS result. Compared to patients with a NEG result, patients with a POS result were less likely to be alive at the end of the study period (14% vs. 35%), and accordingly were more likely to have died of disease (86% vs. 48%) (Fig. 2).

### 3.3. Survival

Compared to the NEG group, the POS group had increased risk of recurrence HR 3.2 (95%CI 0.4, 28.9) and death HR 6.5 (95%CI 0.7, 58.8). Patients with POS results were also significantly more likely to have platinum resistant disease compared to patients with NEG results, 71 vs. 22%, respectively ( $p = 0.007$ ). Accordingly, POS results conferred

Table 1  
Patient characteristics.

Variable	Negative (n = 46)	Positive (n = 7)	P value
Mean age	58.4	59.3	0.86
Mean BMI	28.6	25.2	0.22
Race			0.66
Black	3	0	
White	41	7	
Other	2	0	
GOG status			0.9
0	37	6	
1	8	1	
2	1	0	
Stage			0.27
II	4	2	
III	30	3	
IV	11	2	
Grade			0.85
1	2	0	
2	6	1	
3	38	6	
Histology			0.62
Pap serous	40	6	
Endometrioid	3	0	
Mixed	3	1	

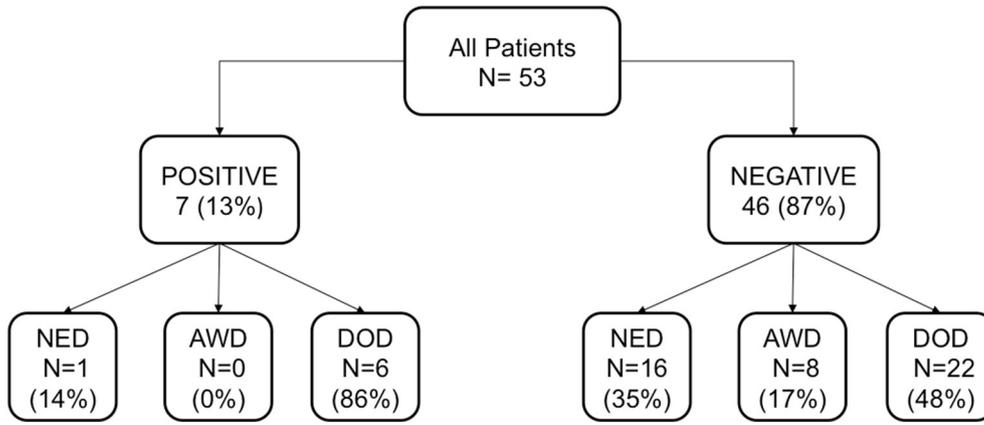


Fig. 2. Summary of disease course.

significantly shorter median PFS at 7 months, compared to 32 months for patients with NEG results ( $p = 0.02$ ). OS was 42 months for patients in the POS group compared with 84 months for patients in the NEG group (Fig. 3).

4. Discussion

Ovarian cancer is devastating to patients and their families and frustrating for the physicians who treat them. Despite advances in therapy and a modest trend toward increased survival, the majority of patients still have advanced stage disease at the time of diagnosis, will recur, and will eventually succumb to their disease. Many patients with a complete response to chemotherapy were found to have residual cancer at the time of second look laparotomy, suggesting that microscopic disease plays an important role in the poor prognosis, even for patients with long disease free intervals. One proposed hypothesis revolves around cancer stem cells that can lie dormant for many years and to lead to delayed recurrences. Better strategies both in identification of these patients and in treatment are necessary before outcomes can be improved. Our investigation sought to determine whether that prognostic information could be provided by a simple and inexpensive test.

The strength of this study is in its prospective design and long study period, which allowed for the detection of a two-fold difference in

overall survival. Additionally, ThinPrep® Cytology Fixative is widely used and readily available. Additional research could be easily conducted at other centers without the need for additional procedures or expensive equipment. Our major limitation was the small size of the study cohort. A larger sample size or multi-center study would allow for sub group analysis and improved the generalizability of results.

Despite its limitations, our study clearly demonstrated that port cytology provides important prognostic information. In the past, GOG studies were stratified by the results of second look laparotomy. This approach proved unsuccessful because it required an invasive procedure, did not impact survival, and patients had more toxic side effects and a decreased quality of life when treated on the basis of those results. IP port cytology offers a non-invasive alternative to the second-look laparotomy and, based on our results, appears predictive of early recurrence and death. This validates previous findings that IP port cytology is both sensitive and specific for the detection of microscopic disease [13] This inexpensive and effective test could serve as an adjunct to imaging studies and tumor markers, which have been shown to be poor methods of assessing microscopic disease status at the end of therapy.

Another historical hurdle for patients who have had a complete response to chemotherapy was the lack of therapeutic options after the completion of primary therapy but before clinical recurrence is diagnosed. In the past, consolidation therapy with traditional cytotoxic

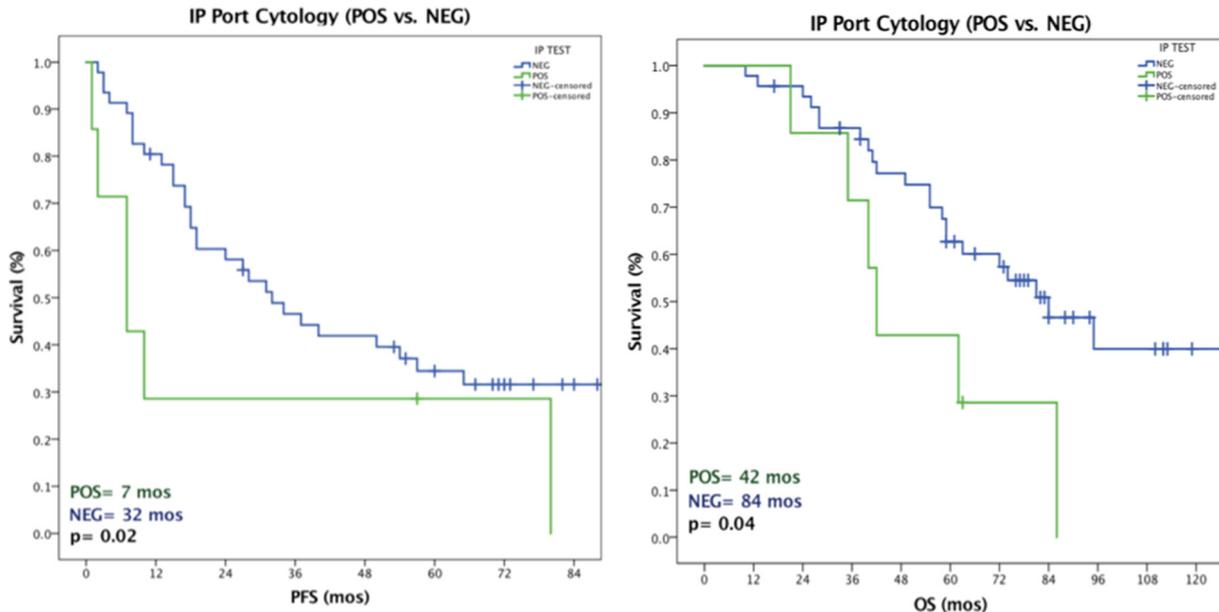


Fig. 3. Median survival.

agents demonstrated a low therapeutic index with lack of a significant survival benefit, yet added toxicity and cost to a patient's care. With the advent of targeted therapeutics such as anti-angiogenic agents and PARP inhibitors that demonstrate a more desirable therapeutic index, earlier treatment in a consolidation or maintenance format may provide improved survival for patients with reduced toxicity. Bevacizumab and PARP inhibitors have demonstrated improved progression free survival over placebo in patients with complete clinical responses. When treated with Olaparib, rucaparib, and niraparib, patients with platinum sensitive recurrent disease had longer progression free survival compared to placebo ranging from 3.6 to 15.5 months, with the largest effects seen with niraparib in patients with germline BRCA mutations. [14–16] Bevacizumab increased PFS in patients receiving primary platinum/taxol therapy after debulking surgery by 3.8 months when continued as maintenance therapy. [17] This has led to FDA approval for these agents as maintenance therapy.

Combining the benefit of non-invasive identification of patients with microscopic residual disease with the addition of newer, less toxic targeted maintenance therapies provides potential promise to improving survival in a well-selected group of patients at high risk for recurrence. As such, IP port cytology may now have clinical relevance by overcoming previous obstacles of invasive detection and toxic, ineffective agents. The prognostic information IP port cytology provides would allow physicians to stratify patients based on risk of recurrence and aid in identification of those who may benefit from clinical trials or consolidation therapy after completion of primary therapy and warrants further study.

#### Author contributions

Dr. Katherine Grette: Data collection, statistical analysis, manuscript writing and review

Dr. Beverly Long: Data collection, manuscript review

Dr. Rodney Rocconi: concept, methodology, statistical analysis, manuscript writing and review

Dr. Michael Finan: concept and methodology, manuscript review

#### Declaration of Competing Interest

None of the authors have a financial interest or conflict of interest regarding the current study.

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