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## **NCI Clinical Announcement**

### **Intraperitoneal chemotherapy for ovarian cancer**

#### **Background**

Epithelial ovarian carcinoma is the leading cause of death from gynecologic malignancies in the developed world. In 2005, it has been estimated that in the United States, 22,220 women will be diagnosed with ovarian cancer, and 16,210 women will die from the disease.<sup>1</sup> To date, no effective screening regimen for ovarian cancer has been identified. More than half of women with ovarian cancer present with advanced-stage disease (FIGO III/IV) at the time of diagnosis.

Epithelial ovarian cancer appears to arise from the epithelial surface of the ovary. Spread of the disease is often by local extension, by intra-abdominal dissemination to other sites within the peritoneal cavity, and by lymphatic spread to pelvic and para-aortic nodes in the retroperitoneum. The recommended treatment includes primary surgery for diagnosis, staging, and cytoreduction, followed by chemotherapy. Unlike many other solid tumors, effective cytoreduction (“debulking”) conveys a survival benefit among with women with ovarian carcinoma.<sup>2,3</sup> The goal of primary surgery is to reduce the burden of ovarian cancer to no or minimal residual disease. The recommended initial chemotherapy is generally a platinum-and-taxane combination given by intravenous infusion every 3 weeks for 6 courses.<sup>4,5</sup>

As residual ovarian cancer after surgery and initial recurrences are primarily confined to the abdomen, intraperitoneal (IP) administration of chemotherapy was first proposed several decades ago.<sup>6</sup> Certain chemotherapeutic agents, including cisplatin and, more recently, paclitaxel, were found to have distinct pharmacokinetic advantages when given via an intraperitoneal route.<sup>7,8,9</sup> These include high intraperitoneal concentration of drug, as well as a longer half-life of the drug in the peritoneal cavity, compared to that observed with intravenous (IV) administration. For cisplatin there was a 10-20-fold greater exposure in the peritoneal cavity over what is achieved with the IV route.<sup>10</sup> In addition, the intraperitoneal administration resulted in prolonged systemic exposure to the chemotherapeutic agents.

### **Recent Trials**

Over the past 10 years, the results of 7 randomized trials assessing the administration of intraperitoneal chemotherapy for first-line treatment of ovarian cancer have become available.<sup>11,12,13,14,15,16,17</sup> (Table 1) These trials represent studies of IP chemotherapy conducted over two decades, with the first patient randomized in 1986. These trials have compared chemotherapy administered via the IV route (conventional therapy) to that administered via a combined IV and IP approach. In all of the trials, the chemotherapy was given after primary surgery. Some of these trials, however, have had complex designs assessing multiple factors in addition to IP treatment. Trial characteristics are summarized in Table 1 and warrant close scrutiny. An 8th trial comparing IP consolidation therapy to no further treatment among women with no evidence of disease

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after primary surgery and adjuvant chemotherapy has been reported.<sup>18</sup> (Table 2) Median survival reported for the control and experimental arms for the eight trials is shown in Tables 3 and 4. The estimated treatment hazard ratios for progression-free survival, based on available data, are shown in Figure 1. The estimated relative death rates are displayed in Figure 2 for 6 of the 8 studies. (The relative death rate was not reported in the studies by Kirmani et al. and Polyzos et al.) On average, IP therapy was associated with a 21.6% decrease in the risk of death (hazard ratio=0.79; 95% confidence interval 0.70-0.89).

Since the expected median duration of survival for women with optimally debulked ovarian cancer receiving standard treatment is approximately 4 years, this size reduction in the overall death rate is expected to translate into about a 12-month increase in overall median survival. The most recent trial, conducted by the Gynecologic Oncology Group and reported by Armstrong et al. in the New England Journal of Medicine, included both IP cisplatin and paclitaxel in the experimental arm. In that study (GOG 172), the improvement in median overall survival was 15.9 months with a treatment hazard ratio of 0.75 (95% confidence interval 0.58-0.97) favoring the IP study arm. The magnitude of improvement in median overall survival associated with IP/IV administration of chemotherapy is similar to that observed with the introduction of either cisplatin or paclitaxel.

### **Toxicity**

The toxicity observed during these trials may be divided into toxicity associated with the presence of an IP catheter, toxicity associated with the IP administration of chemotherapy and the toxicity associated with the chemotherapy itself. A summary of the toxicity

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reported across these 8 studies is shown in Table 5. As might be expected, the risk of infection and fever was higher among patients receiving IP treatment and thus having an IP catheter. In addition, patients receiving IP therapy were more likely to have abdominal pain, nausea, and vomiting. In the most recent study (GOG 172) women on the IP arm experienced greater hematologic, metabolic, and neurologic toxicity than those on the IV arm. The increased toxicity observed in this study may also be due to the IP doses of paclitaxel. In general, however, the toxicity associated with intraperitoneal treatment appeared to be short-term and manageable.

GOG investigators have analyzed the reasons why the prescribed courses of IP chemotherapy on GOG 172 were discontinued.<sup>19</sup> They observed catheter complications in 39 of 118 patients (33%). These included infection in 21 women, catheter blockage in 9, catheter leak in 3, access problems in 5 and drainage per vagina in 1. In addition, they noted reasons for discontinuing IP therapy potentially related to the presence of a catheter among 4 women with abdominal pain, 4 with bowel complication, and 19 women who refused further IP therapy. They did not find any association between the timing of catheter relative to initial surgery or the extent of primary surgery to complication rates, although they did not find that women who underwent left colon resection were less likely to start IP therapy.

### **Health-related Quality of Life (HRQOL)**

HRQOL data are available from GOG 172. Abdominal discomfort improved from baseline to chemotherapy cycle 4 for women on both the IV and IP/IV chemotherapy

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arms, although the improvement was greater among women on the IV arm.<sup>20</sup> They observed better HRQOL among women on the IV arm compared with women randomized to the combined IV/IP arm during and immediately after treatment. These differences disappeared over time, however, so that at one year, HRQOL and pain scores were similar between the two arms except for paresthesias, which were more likely to persist at moderate levels among the patients on the IP/IV arm.<sup>21</sup> These findings suggest that the additional toxicity, with the exception of paresthesias, that may be observed with IP delivery is generally transient and not a long-term issue for most patients.

### **Patient Eligibility**

Patients who may benefit from an IP approach are women with advanced ovarian cancer (FIGO stages III) who have undergone optimal surgical cytoreduction to no or minimal residual (no tumor nodule > 1cm in diameter) disease. Retrospective and prospective cohort studies suggest that 25 to 75% of patients are able to undergo optimal surgical cytoreduction.<sup>3</sup> Factors influencing the success of surgical cytoreduction include younger age, decreased co-morbidity, and the availability of a surgeon and supportive team with expertise in the surgical management of ovarian cancer. The presence of extensive adhesive disease in the abdomen should be considered a relative contraindication to IP therapy, as multiple adhesions may well preclude adequate distribution of IP chemotherapy.

### **Unanswered Questions**

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As Table 1 makes clear, these 8 studies have all evaluated somewhat different experimental treatment regimens, although all utilized IP either cisplatin or IP carboplatin. The use of non-platinum agents varied between the studies, and included cyclophosphamide, anthracyclines, etoposide, and paclitaxel. In 7 of the 8 studies, only cisplatin or carboplatin was given via an IP route, while the most recent study, GOG 172, administered both cisplatin and paclitaxel via an IP route. Fujiwara et al. have recently suggested that substitution of carboplatin for cisplatin may reduce the toxicity of IP platinum.<sup>22</sup> The optimal IP regimen for women with optimally-debulked ovarian cancer remains unclear.

The optimal number of IP treatments is also not known. In SWOG 8501, GOG 114, and GOG 172 the number of IP treatments was often limited due to toxicity. The number of women completing the planned six courses of IP chemotherapy ranged from 71% (GOG 114) to 58% (SWOG 8501) to 42% (GOG 172). (Table 6) Most of the patients who experienced toxicity with IP administration were able to tolerate additional IV chemotherapy. Regardless, intent-to-treat analysis demonstrated a survival benefit even though a large proportion of the patients was unable to complete the full, planned schedule of IP treatments.

We do not know whether women who undergo interval cytoreductive surgery after neoadjuvant chemotherapy, or initial suboptimal cytoreductive surgery followed by several courses of IV chemotherapy, and are then left with no or minimal residual disease, may also derive a survival benefit from IP chemotherapy. In addition, we have

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no data on women with stage IV disease who underwent optimal cytoreductive surgery. As noted above, one study, EORTC 55875, did find a survival benefit associated with consolidation IP therapy among women without clinical evidence of disease after primary surgery and platinum-based chemotherapy. Without additional evidence from well-controlled trials, therefore, we do not know whether women with no or minimal residual disease after surgery and standard platinum-and-taxane IV chemotherapy should be encouraged to consider IP consolidation therapy.

Segna et al. have reported a small series documenting the feasibility of intra-operative administration of chemotherapy for women with gynecologic malignancies.<sup>23</sup>

Several small studies have evaluated intra-operative hyperthermia combined with IP chemotherapy administration.<sup>24,25</sup> To date, however, the use of intra-operative chemotherapy with or without hyperthermia has not been evaluated in a multi-institutional, randomized phase III trial.

There are theoretical concerns that the prolonged half-life of paclitaxel associated with IP administration may delay wound healing.<sup>26</sup> In addition, the administration of IP therapy may exacerbate the development of intra-abdominal adhesions, making subsequent abdominal surgery more risky.

There have been no studies comparing techniques for placement of intraperitoneal catheters, including timing relative to primary surgery, or techniques of administration of chemotherapy in this patient population. As noted above, analysis of data from GOG 172

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suggests that delayed placement of an IP port did not decrease the likelihood of complications.<sup>19</sup> Other surgical procedures, such as hysterectomy, small bowel resection and reanastomosis, and right colon resection, did not affect the initiation of IP chemotherapy.

Better ways of introducing large volumes of fluid into the peritoneal cavity are needed. In addition, novel approaches to prevent fibrotic formation around the IP catheter, as well as to prevent catheter-related mechanical trauma from the catheter to surrounding tissue, such as large and small bowel, are needed.

Further trials are warranted, in particular trials to address reduction of toxicity associated with IP administration.

### **Recommendations for administering IP chemotherapy**

Before primary surgery for presumed advanced stage ovarian cancer, the operating surgeon should discuss with the patient the potential benefits of intraperitoneal chemotherapy, as the surgery may need to be tailored to facilitate subsequent IP chemotherapy. Specifically, performance of a supracervical hysterectomy may avoid surgical entrance into the vagina. If the vagina is opened, then it should be closed with delayed absorbable suture, to avoid leakage of peritoneal instillate from the vaginal defect. Similarly, the abdominal wound can also leak ascites and peritoneal instillate, so it too should be carefully closed with semi-permanent or permanent sutures. In many cases, the port for IP infusion of chemotherapy can be placed at time of primary surgery. Most

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teams of investigators with expertise in the administration of IP chemotherapy recommend the use of a semi-permanent subcutaneous venous access port connected to a single-lumen venous catheter, such as a 9.6 French polyurethane venous access tubing.<sup>27,28</sup> Peritoneal catheters with fenestrations and Dacron cuffs, which had been used in the past, reportedly are associated with a greater incidence of bowel adhesions and erosion into the bowel.

Ports should be located on the inferior thorax at the midclavicular line, placed to avoid irritation from a brassiere. A transverse incision slightly larger than the port should be made overlying the ribs, after which a subcutaneous pocket should be created directly over the fascia covering the ribs. The port should be sutured with permanent 2-0 suture at four corners to the fascia, to prevent rotation or migration and facilitate access via a Huber needle. Next, the catheter should be tunneled under the cutaneous tissue, above the fascia, to a point 6 cm lateral to the umbilicus. At this point, it can be pulled into the peritoneal cavity through a small hole the size of the catheter. The catheter should be cut to a length of about 10 cm, to ensure that it remains in the abdominal cavity, but reduce the risk of adherence to bowel or kinking. The port should then be flushed with 10 cc of heparin (100 units per cc).<sup>19</sup>

Contraindications to placement of an IP port at time of primary surgery include an uncertain pathologic diagnosis, gross bacterial contamination of the peritoneal cavity, serious co-morbidity, and serious intraoperative complications. There is no absolute contraindication to placement of an IP port at the same time as bowel resection and

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reanastomosis, although some surgeons prefer to wait and place the port at a second procedure, in an effort to decrease risks of infection and adhesions. Anaf et al. have described a laparoscopic technique for IP port placement.<sup>29</sup>

Makhija et al. recently reported their own, single-institution retrospective experience of complications associated with the presence of an IP catheter placed as described above for the administration of IP chemotherapy.<sup>28</sup> In their retrospective series, 61 of 313 catheters (19.6%) were placed at time of laparoscopy. Among 301 patients treated between 1989 and 1997 they noted catheter-related complications in 30 women (10%). Of these, 19 women (6.3%) experienced inflow obstruction and 11 (3.6%) experienced infection. Only 21 of 301 (7%) required cessation of IP chemotherapy before its planned completion. In addition, Makhija et al. observed no cases of bowel perforation or small bowel obstruction/ileus.

The optimal volume of infusate is not known. One goal of instilling a large volume of fluid is to ensure that the drug-containing infusate reaches all intra-peritoneal surfaces. One liter of fluid per m<sup>2</sup> of body surface area, up to a maximum of 2 liters, may be a useful target for determining the appropriate volume of infusate for an individual patient.

It seems reasonable to recommend reconstitution of the drugs to be administered via an IP route in one liter of normal saline, followed by infusion of that liter quickly into the abdomen, then infusion of an additional liter of normal saline to facilitate intra-abdominal distribution. Should the patient become uncomfortable for any reason, then the second

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liter need not be entirely infused. There is no need to drain the infused fluid from the abdominal cavity. GOG 172 prescribed the constitution of both paclitaxel and cisplatin in 2 liters of normal saline warmed to 37 degrees Centigrade followed by infusion through a peritoneal catheter as rapidly as possible. After infusion, they encouraged patients to change position at 15 minute intervals for two hours to ensure adequate intra-abdominal distribution.

Patients administered either IP cisplatin or paclitaxel should receive the same supportive-care drugs used with IV administration of these agents. Routine premedications, including H1- and H2-antihistamines and dexamethasone should be given before paclitaxel administration. GOG 172 prescribed dexamethasone 20 mg orally 12 and 6 hours before the infusion of paclitaxel or 20 mg intravenously 30 minutes before the paclitaxel infusion. Both diphenhydramine 50 mg and cimetidine 300 mg (or a suitable alternative) were administered intravenously 30 minutes before the paclitaxel infusion. Hydration and antiemetics should be given before and after cisplatin administration. All GOG protocols in which cisplatin is administered IP mandate the simultaneous administration of at least one liter of normal saline to reduce the risk of cisplatin-induced nephrotoxicity. In addition, delayed nausea is common with IP administration of cisplatin. Antiemetics often need to be maintained for 3 to 4 days after IP infusion.

The largest studies, namely SWOG 8502, GOG 114, and GOG 172, administered an intraperitoneal dose of cisplatin 100 mg/m<sup>2</sup> given every 3 weeks. It would seem reasonable, therefore, to consider the same dose for treatment of patients off protocol,

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with appropriate dose reduction for toxicity. Patients should be routinely questioned about potential neurotoxicity, and undergo immediate dose reduction for neurotoxicity  $\geq$ CTCAE grade 1. In addition, delivery of IV paclitaxel at a reduced dose (135 mg/m<sup>2</sup>) with a 24-hour infusion pump can reduce the risk of neurotoxicity.

Patients with malignant ascites who are otherwise candidates for IP chemotherapy should undergo drainage of their ascites followed by IP installation of the infusate. In order to keep the vascular compartment full, however, individual patients may need additional IV fluid so that the total volume of fluid administered balances that of the ascites removed. If a woman undergoes removal of 3 liters of ascites, followed by 2 liters of IP infusate, then she will also need at least an additional liter of IV fluid over the next 24 hours.

The optimal management of toxicities associated with IP administration of chemotherapy is not well established. GOG 172 mandated reduction of the dose of IP drug for patients reporting grade 2 abdominal pain. As noted above, patients should be regularly assessed for potential neurotoxicity, with immediate dose reduction of cisplatin for any degree of neurotoxicity. In GOG 172, treatment was held for grade 3 or 4 peripheral neuropathy and not restarted until neuropathy resolved to grade 2 or less. Again in GOG 172, patients who experienced recurrent grade 2 abdominal pain after dose reduction or who experienced grade 3 abdominal pain were switched to IV chemotherapy. If creatinine rose to greater than 2.0 mg/day, then creatinine clearance was measured. Treatment was held if creatinine clearance was less than 50 cc/min and was resumed only when creatinine clearance was greater than 50 cc/min. There is no evidence that IP cisplatin is

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more nephrotoxic than IV cisplatin. As noted above, all GOG protocols in which cisplatin is administered IP mandate the simultaneous administration of at least one liter of normal saline to reduce the risk of cisplatin-induced nephrotoxicity.

If a patient is not able to tolerate infusion of the treatment volume, due to unacceptable pain or extremely slow infusion, then the IP route should be abandoned and the patient treated with IV chemotherapy. Similarly, if the patient experiences severe complications related to the presence of an IP catheter, such as intra-abdominal infection, prolonged ileus, bowel obstruction, or bowel perforation, then the complication should be managed appropriately and the route of chemotherapy switched from IP to IV. In general, a malfunctioning IP catheter should not be replaced; instead the physician should switch to IV chemotherapy. IP catheters should be removed at the completion of IP chemotherapy as the patient's medical status permits. In general, IP ports can be easily removed under local anesthesia in the office.

### **Summary**

Based on the results of these randomized phase III trials, a combination of IV and IP administration of chemotherapy conveys a significant survival benefit among women with optimally debulked epithelial ovarian cancer, compared to IV administration alone. While it is not possible to specify a precise regimen, the three largest studies with the greatest survival advantage delivered cisplatin 100 mg/m<sup>2</sup> IP. The two most recent trials also included taxanes. In all the published studies, the chemotherapy regimens mandated modification based on patient tolerance.

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The benefit appears to be approximately a 12-month improvement in median overall survival (range 0-16 months). Of note, the magnitude of improvement in survival is similar to that noted with the introductions of cisplatin and of paclitaxel in the treatment of women with ovarian cancer. Combined IP/IV administration of chemotherapy, however, may also be associated with a significantly increased short-term risk of toxicity compared with IV chemotherapy. In general, however, the toxicity is short-term and manageable.

Effective surgical debulking is critical to long-term survival for ovarian cancer. Women undergoing surgery for presumed ovarian cancer, therefore, should undergo surgery by a gynecologic oncologist or a surgical team with expertise in the staging and cytoreduction of ovarian cancer. After primary surgery, women with optimally-debulked FIGO stage III ovarian cancer should be counseled about the clinical benefit associated with combined IV and IP administration of chemotherapy. Based on the most recent trials, strong consideration should be given to a regimen containing IP cisplatin (100 mg/m<sup>2</sup>) and a taxane, whether given by an IV only or IV plus IP.

Women with epithelial ovarian cancer and their physicians should be encouraged to participate in prospective clinical trials, in order to identify better treatment for this disease.

Table 1. Randomized trials comparing IV versus IP or IP/IV first-line treatment of ovarian cancer

Study identifier/ year published	Control regimen	Experimental regimen	Eligible patients	Number of patients
Kirmani et al., 1994	Cisplatin 100 mg/m <sup>2</sup> IV; Cyclophosphamide 600 mg/m <sup>2</sup> Q 3 weeks x 6	Cisplatin 200 mg/m <sup>2</sup> IP; etoposide 350 mg/m <sup>2</sup> IP Q 4 weeks x 6	Stage IIC-IV	62
SWOG 8501/ GOG 104 Alberts et al., 1996	Cisplatin 100 mg/m <sup>2</sup> IV; Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks x 6	Cisplatin 100 mg/m <sup>2</sup> IP; Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks x 6	Stage III, ≤ 2 cm residual	546
Polyzos et al., 1999	Carboplatin 350 mg/m <sup>2</sup> IV; Cyclophosphamide 600 mg/m <sup>2</sup> IV Q 3 weeks x 6	Carboplatin 350 mg/m <sup>2</sup> IP; Cyclophosphamide 600 mg/ m <sup>2</sup> IV Q 3 weeks x 6	Stage III	90
Gadducci et al., 2000	Cisplatin 50 mg/m <sup>2</sup> IV; Cyclophosphamide 600 mg/m <sup>2</sup> IV; Epidoxorubicin 60 mg/m <sup>2</sup> IV Q 4 weeks x 6	Cisplatin 50 mg/m <sup>2</sup> IP; Cyclophosphamide 600 mg/ m <sup>2</sup> IV; Epidoxirubicin 60 mg/m <sup>2</sup> IV Q 4 weeks x 6	Stage II-IV, < 2 cm residual	113
GOG 114/ SWOG 9227 Markman et al., 2001	Cisplatin 75 mg/m <sup>2</sup> IV Paclitaxel 135 mg/m <sup>2</sup> (24 hr) IV Q 3 weeks x 6	Carboplatin (AUC9) IV q 28 days x 2; Cisplatin 100 mg/ m <sup>2</sup> IP; Paclitaxel 135 mg/m <sup>2</sup> (24 hr) IV q 3 weeks x 6	Stage III, ≤ 1 cm residual	462
Yen et al., 2001	Cisplatin 50 mg/m <sup>2</sup> IV; Cyclophosphamide 50 mg/m <sup>2</sup> IV; Epidoxorubin/ Doxorubicin 50 mg/m <sup>2</sup> IV Q 3 weeks x 6	Cisplatin 100 mg/m <sup>2</sup> IP Cyclophosphamide 500 mg/m <sup>2</sup> IV; Epidoxirubicin/ Doxorubicin 50 mg/m <sup>2</sup> IV Q 3 weeks x 6	Stage III, ≤ 1 cm residual	118
GOG 172 Armstrong et al., 2006	Cisplatin 75 mg/m <sup>2</sup> IV; paclitaxel 135 mg/m <sup>2</sup> (24 hr) IV Q 3 weeks x 6	Paclitaxel 135 mg/m <sup>2</sup> (24 hr) IV; Cisplatin 100 mg/m <sup>2</sup> IP; Paclitaxel 60 mg/m <sup>2</sup> IP on day 8 Q 3 weeks x 6	Stage III, ≤ 1 cm residual	415

Notes: SWOG 8501/GOG 104 was conducted under the auspices of the NCI/Bristol Myers Squibb (BMS) cisplatin cooperation program. GOG 114/SWOG 9227 and GOG 172 were conducted under the auspices of the NCI/BMS Cooperative Research and Development Agreement for paclitaxel.

Table 2. Randomized trials comparing surveillance to IP consolidation treatment

Study identifier/ authors/ year published	Control regimen	Experimental regimen	Eligible patients	Number of patients
EORTC-55875, Piccart et al., 2003	Surveillance	Cisplatin 100 mg/m <sup>2</sup> IP Q 3 weeks x 4	Stage IIB-III in pathologic complete response following platinum-based primary treatment	153

Table 3. Median survival time for randomized trials comparing IV versus IV/IP first-line treatment of ovarian cancer

Study identifier/authors/ year published	Number of patients	Median duration of survival for control regimen (months)	Median duration of survival for experimental regimen (months)
SWOG 8502/GOG 104, Alberts et al., 1996	546	41	49
Polyzos et al., 1999	90	52	63
Gadduci et al., 2000	113	25	26
GOG 114/SWOG 9227/ ECOG GO114 Markman et al, 2001	462	51	67
Yen et al., 2001	118	48	43
Armstrong et al., 2006	415	50	66

Table 4. Median survival time for randomized trial comparing surveillance to IP consolidation treatment

Study identifier/ year published	Number of patients	Median survival duration for control regimen (months)	Median survival duration for experiment regimen (months)
EORTC 55875, Piccart et al, 2003	153	78	91

Table 5. Reported toxicity

Category	Symptom	Study	IV (%)	IP/IV (%)	P-value
Auditory					
	Hearing loss ( $\geq$ Grade 2)	Alberts et al.	15	5	P<0.001
	Tinnitus ( $\geq$ Grade 2)	Alberts et al.	14	7	P=0.01
Blood/bone marrow					
	Anemia ( $\geq$ Grade 3)	Alberts et al.	25	26	ns
		Gadducci et al.	8	6	nr
		Kirmani et al.	3	7	nr
		Yen et al.	12	7	ns
	Granulocytopenia ( $\geq$ Grade 3)	Alberts et al.	69	56	P=0.002
	Leukopenia ( $\geq$ Grade 3)	Alberts et al.	50	40	P=0.04
		Armstrong et al.	64	76	P<0.001
		Gadducci et al.	19	24	nr
		Kirmani et al.	21	19	nr
		Markman et al.	62	77	nr
		Polyzos et al.	18	5	P<0.01
		Yen et al.	21	10	P=0.033
	Thrombocytopenia ( $\geq$ Grade 3)	Alberts et al.	9	8	ns
		Armstrong et al.	4	12	P<0.001
		Gadducci et al.	2	0	nr
		Kirmani et al.	0	5	nr
		Markman et al.	3	49	nr
		Polyzos et al.	10	3	P<0.09
		Yen et al.	10	7	ns
Constitutional symptoms					
	Fatigue ( $\geq$ Grade 3)	Armstrong et al.	4	18	P<0.001
		Markman et al.	1	3	nr
	Fever ( $\geq$ Grade 2)	Alberts et al.	5	6	ns
		Gadducci et al.	9	4	nr
	Fever ( $\geq$ Grade 3)	Armstrong et al.	4	9	P=0.02
		Markman et al.	1	3	nr
Gastrointestinal	$\geq$ Grade 3	Armstrong et al.	24	46	P<0.001
		Markman et al.	17	37	nr
		Gadducci et al.	26	37	nr
	Nausea/ vomiting (Grade 2)	Piccart et al.	NA	82	na
Infection	Grade 1	Piccart et al.	NA	26	na
	$\geq$ Grade 3	Armstrong et al.	6	16	P=0.001
		Markman et al.	1	4	nr
Metabolic	$\geq$ Grade 3	Markman et al.	1	10	nr
	Hepatic	Armstrong et al.	<1	3	P=0.05
	Renal	Armstrong et al.	2	7	P=0.03

Category	Symptom	Study	IV (%)	IP/IV (%)	P-value
	Creatinine clearance ( $\geq$ Grade 3)	Markman et al.	1	5	nr
	Creatinine clearance (Grade 2)	Piccart et al.	NA	45	na
Neurology					
	Neuromuscular effects at end of treatment ( $\geq$ Grade 2)	Alberts et al.	25	15	P=0.02
	Neurotoxicity (Grade 2 or 3)	Piccart et al.	NA	15	na
	Neurotoxicity ( $\geq$ Grades 3)	Armstrong et al.	9	19	P<0.001
		Markman et al.	9	12	nr
Pain					
	Abdominal pain (Grade 1 or 2)	Piccart et al.	NA	38	na
	Abdominal pain ( $\leq$ Grade 2)	Alberts et al.	2	18	P<0.001
	Abdominal pain ( $\geq$ Grade 3)	Armstrong et al.	1	11	P<0.001

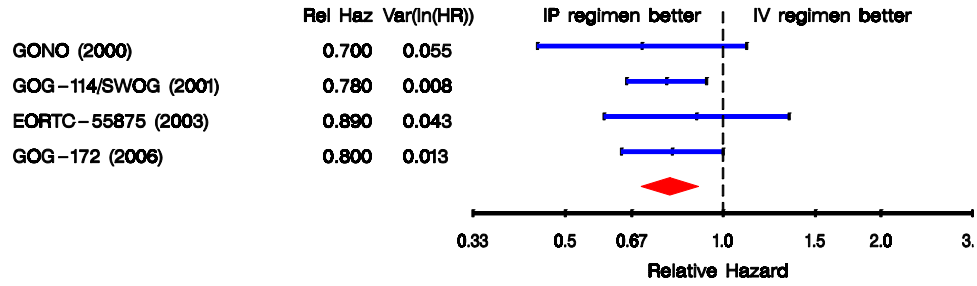
Abbreviations: nr=not reported; ns=not significant; na=not applicable

Table 6. Completion rate for prescribed courses of chemotherapy (%)

Study identifier/author/year of publication	IV regimen (%)	IP/IV regimen for IP administration (%)
SWOG 8501/GOG 104, Alberts et al., 1996	58	58
GOG 114/SWOG 9227 ECOG GO114, Markman et al., 2001	86	71
Gadducci et al., 2000	96	65
EORTC 55875, Piccart et al., 2003	NA	56
GOG 172, Armstrong et al., 2006	90	42

Abbreviation: NA=not applicable

### Treatment Hazard Ratios for PFS Intraperitoneal vs Intravenous Therapy



$I^2$  heterogeneity (3 d.f.) = 0.629, p=0.89

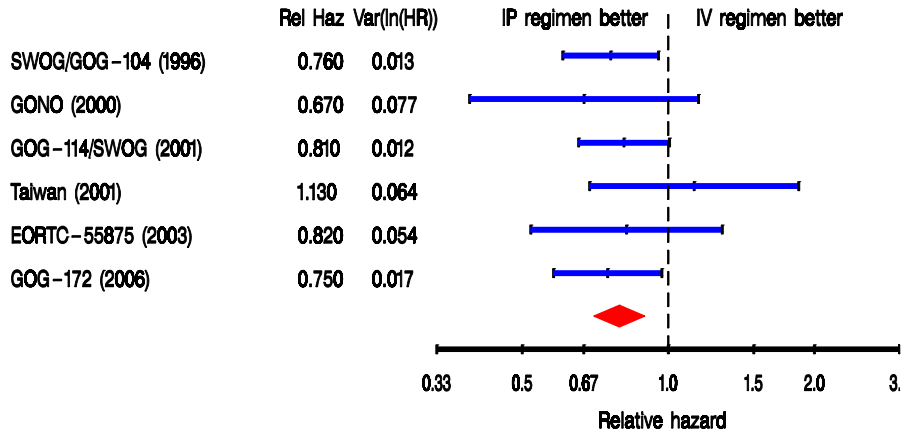
The red diamond shows the pooled estimate of the treatment hazard ratio for PFS: 0.79, 95% confidence interval (0.70, 0.90).

PFS hazard ratios are not available from the published report on SWOG-8501/GOG 104 or the studies of Kirmani et al., Polyzos et al., and Yen et al.

PFS hazard ratio is not reported for the study of Gadducci et al. but it is calculated from the available data reported.

Figure 1

### Treatment Hazard Ratios for Overall Survival Intraperitoneal vs Intravenous Therapy



$I^2$  heterogeneity (5 d.f.) = 2.70, p=0.75

The red diamond shows the pooled estimate of the treatment hazard ratio for survival: 0.79, 95% confidence interval (0.70, 0.89).

Hazard ratio was not reported for the study of Gadducci et al. but it is calculated from the available data reported.

Hazard ratio is not available from the studies of Kirmani et al. and Polyzos et al.

Figure 2

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