Published in final edited form as:
Gynecol Oncol. 2011 November ; 123(2): 346–350. doi:10.1016/j.ygyno.2011.07.099.

A prospective, randomized trial of integrative medicine for women with ovarian cancer☆,,☆☆

Patricia L. Judson[a,*], **Elizabeth L. Dickson**[b], **Peter A. Argenta**[b], **Yin Xiong**[a], **Melissa A. Geller**[b], **Linda F. Carson**[b], **Rahel Ghebre**[b], **Amy L. Jonson**[b], and **Levi S. Downs Jr.**[b]

[a]H. Lee Moffitt Cancer Center & Research Institute, Department of Women's Oncology, USA

[b]University of Minnesota, Department of Obstetrics, Gynecology and Women's Health, USA

Abstract

Objectives—Despite increased use of integrative medicine in cancer therapy, little data exist on its efficacy. This prospective, randomized, pilot trial sought to evaluate the feasibility of combined modality integrative medicine (CM-IM) in women with ovarian cancer (OvCA) and evaluate its effects on quality of life (QoL), chemotherapy toxicity and immunologic profiles.

Methods—Women with newly diagnosed OvCA requiring chemotherapy were offered enrollment. Those randomized to the experimental arm received hypnosis, therapeutic massage and healing touch with each cycle of chemotherapy. The control arm received chemotherapy without CM-IM. All patients completed QoL questionnaires prior to cycles 1, 3 and 6, and 6-months after chemotherapy. Immunologic profiles were measured. Statistical analysis was based on intent-to-treat. Student's *t*-test and Fischer's exact-test were used to determine differences.

Results—Forty-three women enrolled. All women randomized to CM-IM were successfully treated. There were no statistical differences between the groups in age, stage, grade, histologic cell type, CA125 levels, or surgical cytoreductive status. There was no difference in overall QoL measurements. Re-hospitalization rates, treatment delays, anti-emetic use, and infection rates were similar. Immunologic profiles revealed no difference between arms for WBC or salivary IgA levels. Women receiving CM-IM had consistently higher levels of CD4, CD8 and NK cells, although this did not reach statistical significance.

Conclusions—Prospective clinical evaluation of integrative medicine for women with gynecologic malignancy is feasible. This first, pilot study of CM-IM in gynecologic oncology demonstrated no improvement in QoL or chemotherapy toxicity. Integrative medicine-associated improvements in immunologic profiles warrant further investigation.

Keywords

Ovarian cancer; Prospective; Randomized; Therapeutic massage; Healing touch; Integrative medicine

☆This research was supported by grants from the Randy Shaver Cancer Research Fund and by a Sime Research Fellowship in Complementary and Alternative Medicine through the Center for Spirituality & Healing, University of Minnesota.

☆☆Research was presented at the Society of Gynecologic Oncologists 41st annual meeting, 3/2010.

*Corresponding author at: Department of Women's Oncology, Moffitt Cancer Center, USA. Fax: +1 813 745 5543. Patricia.Judson@moffitt.org (P.L. Judson).

Conflict of interest statement
The authors declare that there are no conflicts of interest.

Background

Women with the diagnosis of ovarian cancer typically receive primary surgery followed by prolonged and recurrent exposure to toxic chemotherapy, with poor long-term survival prospects. Subsequently, these women report high levels of psychosocial stress which may in turn reduce their ability to cope, both mentally and physically, with their condition [1] In a prospective study of 151 women with ovarian cancer, 78% of patients had moderate to high levels of psychological distress as defined by depression, anxiety and emotional lability [2].

Increasingly, patients with cancer, and especially women with cancer, are turning to integrative medicine [IM] (or complementary and alternative medicine [CAM]) to address unmet needs during therapy [3]. Some authors report that up to 80% of all patients with cancer and 44% of women with gynecologic cancers use some form of IM during the course of their therapy [4–6]. The National Center for Complementary and Alternative Medicine (NCCAM) defines CAM (IM) as a group of diverse medical and health care systems, practices and products that are not generally considered part of conventional medicine including but not limited to: nutritional supplements, vitamins, hypnosis, massage, acupuncture, healing touch, and guided imagery [7]. NCCAM categorizes CAM into five major groups: whole medical systems, mind-body medicine, biologically based practices, manipulative and body-based practices, and energy medicine.

Though outcome data for integrative therapies, particularly in gynecologic malignancies, are scarce, most authors report a positive impact on both physical and emotional well-being [5]. In the largest study to include women with gynecologic cancers, Fasching et al. observed that of all women using IM, 35.1% reported a deterioration of their health status during treatment for cancer, compared to 50.1% of women not using IM [6].

Though multiple IM techniques have evolved, most research suggests that the benefit of integrative therapies derive from supporting healing and coping mechanisms. Alternatively however, the benefits of IM may derive from enhancement of immune modulators noted to be improved after some IM strategies [8,9]. For example, cytotoxic immune response by T cells (including CD_4 and CD_8), as well as NK cells plays a key role in the recognition and destruction of malignant cells, and have been reported to be improved following massage therapy. NK cell cytotoxic activity is decreased in multiple advanced cancers, including gynecologic malignancies [10]. An increase in NK cells was shown to have a beneficial impact on survival in malignant melanoma patients [11]. In a study of patients with Stage III colon cancer, increases in CD_{56}, CD_8 and CD_4 levels were correlative with disease free survival [12].

For the purposes of this study, we were looking for a global effect of IM. To maximize the likelihood of seeing a treatment effect we selected 3 IM interventions; one each from 3 of the 5 NCCAM identified major categories including: hypnosis (from mind–body medicine), therapeutic massage (from manipulative and body based practices), and healing touch (from energy medicine) as these therapies have been shown in small studies to be beneficial for enhancing QoL, while reducing pain, depression, anxiety, and chemotherapy side effects and for improving immunologic profiles. Our main objective was to evaluate the feasibility of a prospective clinical trial of a select number of IM interventions in the gynecologic oncology population. Furthermore, we sought to determine if women receiving chemotherapy and combined modality IM had an improved quality of life (QoL); reduced chemotherapy side effects; or significant changes to immunologic profiles.

Materials and methods

This prospective, randomized, controlled trial was approved by the Internal Review Board of the University of Minnesota and was open to recruitment from 2006 to 2009. Patients were eligible if they had newly diagnosed ovarian, primary peritoneal, or fallopian tube carcinoma at any stage or histology, and were scheduled to receive at least 6 cycles of taxane and platinum chemotherapy. Patients were excluded if they had a previous cancer other than non-melanoma skin cancer, had previously received chemotherapy, had active substance abuse, schizophrenia, or were pregnant or lactating. Eligible patients made informed consent and were randomized to chemotherapy alone or chemotherapy with CM-IM.

All therapies were administered at the University of Minnesota Medical Center. Patients received either intravenous paclitaxel and carboplatin on an every 3 week basis, or a combination of intravenous and intraperitoneal paclitaxel and cisplatin.

Women randomized to the control arm received standard antiemetic therapy and bone marrow support. While not prohibited, the women in the control arm were encouraged to not seek out IM therapies. Access to hospital or regional support groups was not influenced in either group. The control arm received their chemotherapy in the standard fashion while in a chemotherapy recliner or bed. IM modalities involve increased attention to the recipient, this added attention is thought to be a part of the healing process and decreasing stress, both may enhance immune function. The investigators recognize that the attention may be a factor in favorable outcomes.

Women randomized to the IM arm of the trial received clinical hypnosis, massage therapy, and healing touch.

Clinical hypnosis was performed with each chemotherapy cycles. Cycles one, two, and four were with a hypnotist. The hypnosis sessions were audio recorded and the patient was given a headset to listen to the session when desired and at cycles 3, 5 and 6 of chemotherapy. The content was semi-structured to tailor to each patient's needs. The patient's history with hypnosis or related activities such as medication, relaxation training, and visualization was assessed. Each patient was asked to identify the one or two most problematic concerns about diagnosis, chemotherapy, or medical treatment, as well as their 'antidotes' to these concerns. Prior to the first hypnosis meeting the patient was screened for exclusionary criteria and provided a pamphlet titled "Questions and Answers about Clinical Hypnosis." This pamphlet was reviewed prior to the first session. Credentials and qualifications of the hypnotherapist were provided to the patient. The first session was 60 min and established rapport between the patient and therapist; it assured that the patient understood the information about hypnosis, customized the hypnotic protocol to meet the needs of the patient, and engaged the patient in hypnosis. The two subsequent hypnosis sessions were 30 min in length and performed before cycles 2 and 4 of chemotherapy. At these sessions, the patient's mood, functioning, and coping mechanisms were assessed. The experience with hypnosis was reviewed, and the patients were asked what worked, what did not work, and what discoveries were made about the use of hypnosis to heal.

Therapeutic massage was administered by a single provider with each cycle of chemotherapy for 30 min. Massage therapy was performed with the patient resting in a chemotherapy recliner. Standard manual massage techniques were employed over the head, neck, shoulders, back, hands and/or feet. Intensity and rapidity of massage movements were individualized based on the patient's comfort level.

Healing touch was administered with each cycle of chemotherapy. Prior to the first session the women in the treatment arm were given a handout regarding healing touch. Followingthe massage therapy session, a certified practitioner in healing touch performed the maneuvers for 30 min. One practitioner was used throughout the trial. The practitioner performed a structured interview with the patient both as a verbal assessment and an energy/physical assessment; this assessment was done both with a pendulum held a few inches over each of the seven main energy centers (chakras) and by running the hand slowly through the patient's energy field a few inches off the body. Interventions included: chakra connection (an energy technique used to facilitate energy flow through the major chakras for increased health and vitality), magnetic passes (moving the hands over the body without touching, and using the fingers to "comb" over the energy field of the patient to facilitate the removal of blockages in the energy system) and mind clearing (a technique used to promote energy flow and relaxation in order to clear the mind, allowing the patient to reach a state of peacefulness). Each session was tailored to the patient to address their individual needs, such as pain management and anxiety.

At each chemotherapy visit, patients underwent a performance assessment and laboratory testing including evaluation of total white blood cell (WBC) count with differential, T and B-cell count in mm^3 (including T-Helper/inducer, CD_4 and CD_8 cells), salivary IgA levels in mg/dl and NK count in mm^3. These immune parameters were selected as there is previous data validating their reproducibility. An objective assessment of quality of life (QoL) using the FACT-O and Mental Health Inventory was obtained prior to chemotherapy cycles 1, 3, and 6, as well as 6 months after chemotherapy was completed. The FACT-O survey is a brief, validated measure of physical, emotional, functional and social well-being in ovarian-type cancer patients [13]. The Mental Health Inventory (MHI) is a 39 item questionnaire and seeks to evaluate psychological well being and distress [14]. Information on delays in chemotherapy protocol, infection rate, re-hospitalization rate and number and type of anti-emetics used via pill count and patient report was collected prospectively. Demographic information collected included age, stage and grade of disease, histologic cell type, CA 125 levels, and co-morbid conditions.

This was a pilot study to assess the feasibility of performing IM in women receiving treatment for gynecologic malignancy. A power analysis was not performed to detect a difference. Analysis was conducted as intent-to-treat. All randomized patients were included, regardless of number of courses of chemotherapy, IM therapy or survival. Descriptive analysis was undertaken to confirm that the treatment and control groups were not statistically different. Repeated analysis of variance measures were used to evaluate effect of time and treatment interactions. Differences in CD4, CD8, NK cells, and IgA levels were analyzed with unpaired t-tests.

Results

A total of 43 women with ovarian, primary peritoneal, or fallopian tube cancer were recruited into the study of which 20 were randomized to the control arm and 23 to the treatment arm. One patient withdrew consent prior to receiving any chemotherapy or IM therapy and was removed from analysis.

Multimodality IM was both feasible and acceptable to all women enrolled. All women in the IM arm of the trial received all prescribed IM interventions. All sessions were able to be scheduled with the practitioners, the IM interventions were able to be administered in the standard chemotherapy chairs. The IM interventions did not interfere with the delivery of chemotherapy.

Patient characteristics are listed in Table 1. There was no statistical difference between the groups with regard to age, stage, grade of tumor, histologic subtype, CA125 level at the initiation or completion of chemotherapy, and surgical cytoreductive status.

Quality of life

The average score for the FACT-O and MHI surveys were analyzed at baseline, prior to chemotherapy cycle 3 and 6 and 6-months following chemotherapy. When comparing the control versus treatment arms, there was no statistically significant difference at any time point (Table 2).

Chemotherapy toxicity

In the IM arm, 7/22 (31.8%) patients experienced chemotherapy treatment delays compared to 8/20 (36.4%) in the control arm. Reasons for delay in chemotherapy included partial small bowel obstruction (SBO), and bone marrow toxicity/compromise and were similar between the groups. The incidence of admission after chemotherapy was 6/22 (27.2%) in the IM arm and 5/20 (25%) in the control arm. The most common reason for admission after chemotherapy was neutropenia (1patient fromeacharm)and nausea/vomiting andpartialSBO(1patient from each arm). Of the 22 patients in the IM arm, 3 (13.6%) patients had infections after chemotherapy (pneumonia, URI, cellulitis) versus 2/20 (9.1%) patients in the control arm (colitis and sinus infection).

There was not a significant difference in the amount of anti-emetic use between the two groups (5.95 prescriptions on average in the IM arm and 4.75 prescriptions in the control arm, p=0.09). The total dosage of anti-emetics received by patients in the two arms of the study was not statistically different (604.2 mg on average in the IM arm and 453.2 mg in the control arm, p=0.12).

Immunologic profiles

Compared to controls, women receiving CM-IM had consistently higher levelsof CD4, CD8 andNK cell countsat each cycle of chemotherapy (Fig. 1). These values did not, however reach statistical significance. CD4 count (average, control 680 mm^3, IM 811 mm^3, p=0.20), CD8 count (average, control 281 mm^3, IM 364 mm^3, p=0.07), NK cell count (average, control 213 mm^3, IM 244 mm^3, p=0.51). There was no statistically significant difference in WBC count (average, control 5653, IM 6144, p=0.38), or IgA level (average, control 14.07 mg/dl, IM 8.66 mg/dl, p=0.12).

Discussion

In this pilot study of combined-modality IM interventions we have shown that IM is well tolerated by patients and did not interfere with the delivery of chemotherapy. However, it did not appear to change QoL, complication rates or the immunologic parameters evaluated.

The lack of change to QoL or other parameters evaluated in IM versus control patients receiving chemotherapy may indicate a lack of significant activity of our selected IM techniques. However, it may also reflect: the low power of this study to detect small but potentially relevant differences in the parameters measured; the absence of blinding or placebo in the control arm; the endpoints selected; or the IM interventions used.

We believe our selection of IM interventions for this pilot study was appropriate. Clinical hypnosis, an altered state of consciousness resulting from selective deployment of attention onto a focal goal and away from stimuli perceived as peripheral, was chosen for this study because it has been shown, in combination with other psychological interventions, to

enhance the quality of life of patients with cancer [15,16]. Hypnosis has also been reported to significantly reduce chemotherapy-induced nausea and vomiting in pediatric patients [17]. In case studies of patients with breast or gynecologic cancer, hypnosis has been shown to help reduce pain, decrease depression and anxiety, and ameliorate chemotherapy side effects [18].

Massage therapy is manipulation, rubbing and kneading of the body's muscle and soft tissue. Massage therapy was selected for this study as it has been shown in breast cancer patients and HIV positive men to effect cellular changes in immune function including an increase in white blood cell (WBC) counts and natural killer (NK) cells [8,9]. A review of randomized trials on massage therapy for cancer palliation and supportive care suggests that massage can alleviate a wide range of symptoms: pain, nausea, anxiety, depression, anger, stress, and fatigue. However, the methodology used in these trials was poor and therefore definitive conclusions could not be made [19,20].

Healing touch is a biofield therapy that employs a holistic, energy-based approach to healing and health. While the mechanism by which healing touch promotes functioning is still unknown, we selected this therapy because it has been reported that healing touch can decrease anxiety levels and increase immune function in patients with non-malignant conditions [21,22]. In symptomatic patients, massage therapy and healing touch appear to be effective in reducing mood disturbance and fatigue in patients receiving chemotherapy [23].

Data from the FACT-O and MHI 6 month follow up surveys were not statistically different between IM and control groups. However, when analyzing the FACT-O data, there was an improvement in overall scores after 6 months in both groups of patients. This suggests that both arms of the study had improvement in their perceived QoL after chemotherapy was completed, regardless of receiving CM-IM interventions. At 6 months of follow up there was also noted to be improvement in FACT-O values over baseline for both groups, supporting the theory that once chemotherapy is complete, QoL can return to baseline or even improve.

While it may be surprising that there was an absence of an improvement in QoL between the two treatment arms in this study as shown in previous studies, this may reflect that most previous studies failed to include a control arm and may therefore erroneously attribute the post-therapy rise in QoL to IM interventions. In fact, most recent chemotherapy trials which evaluate QoL over longer duration demonstrate significant improvement from baseline at 6 months post-therapy. This effect was observed in both arms of GOG 172 despite significant decreases in QoL during therapy, particularly among patients receiving IP therapy, and residual neuropathy that persisted well past the 6 month follow-up [24]. These data together suggest that QoL may be most influenced by time and experience which diffuse a patient's uncertainty surrounding a new diagnosis. In turn this might imply that improved education immediately after diagnosis may be an effective means to achieve the same impact on QoL. It is unclear if IM interventions following completion of therapy would accelerate the time to return to baseline or improved QoL.

This study compared the use of IM therapies to usual care outcomes. IM modalities involve increased attention to the recipient. This added attention is thought to be a stress-reducing part of the healing process and thus enhancing to immune function — both may enhance immune function. The investigators recognize that the attention may be a factor in favorable outcomes. Women in the control arm were not prohibited, but were encouraged to not engage in IM therapies while on the trial. We did not screen for the use of outside IM therapies in either arm, this may serve as a source of bias.

There have been studies in patients with cancer which demonstrate a link between overall survival and improved immunomodulators [10–12]. Our data show that the average CD4, CD8 and NK cell levels were higher at almost every course of chemotherapy (Fig. 1). These data are enticing and deserves further investigation in a larger trial.

We demonstrate that the use of IM is feasible as an adjunct to standard of care for women with gynecologic malignancies. Our inability to demonstrate a significant impact of IM may reflect the limited power of this pilot study to detect small, but clinically significant, differences.

References

1. Eschiti VS. A model of CAM use by women with female-specific cancers. J Psychosoc Nurs Ment Health Serv. 2008; 46(12):50–7. [PubMed: 19133495]
2. Kornblith AB, Thaler HT, Wong G, et al. Quality of Life of women with ovarian cancer. Gynecol Oncol. 1995; 59:231–42. [PubMed: 7590479]
3. Von Gruenigen VE, Frasure HE, Jenison EL, Hopkins MP, Gil KM. Longitudinal assessment of quality of life and lifestyle in newly diagnosed ovarian cancer patients: the roles of surgery and chemotherapy. Gynecol Oncol. 2006; 103:120–6. [PubMed: 16556458]
4. Bernstein BJ, Graso T. Prevalence of complementary and alternative medicine use in cancer patients. Oncology. 2001; 15(10):1267–72. [PubMed: 11702957]
5. Eschiti VS. Lessons from comparison of CAM use by women with female-specific cancers to others: it's time to focus on interaction risks with CAM therapies. Integr Cancer Ther. 2007; 6(4): 313–44. [PubMed: 18048881]
6. Fasching PA, Theil F, Nicolaisen-Murmann K, et al. Association of complementary methods with quality of life and life satisfaction in patients with gynecologic and breast malignancies. Support Care Cancer. 2007; 15(11):1277–84. [PubMed: 17333294]
7. National Center for Complementary and Alternative Medicine. [Accessed May 2010.] What is CAM?. 2008. http://nccam.nih.gov/health/whatiscam
8. Ironson G, Field T, Scafidi F, Hashimoto M, et al. Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. Int J Neurosci. 1996; 84:205–17. [PubMed: 8707483]
9. Hernandez-Reif M, Field T, Ironson G, et al. Natural killer cells and lymphocytes increase in women with breast cancer following massage therapy. Int J Neurosci. 2005; 115(4):495–510. [PubMed: 15809216]
10. Garzetti GG, Cignitti M, Marchegiani F, et al. Natural killer cell activity in patients with gynecologic malignancies: correlation with histologic grading and stage of disease. Gynecol Obstet Invest. 1992; 34(1):49–51. [PubMed: 1526531]
11. Fawzy FI, Fawzy NW, Hyun CS, et al. Malignant melanoma. Arch Gen Psychiatry. 1993; 50:681–9. [PubMed: 8357293]
12. Holcoombe RF, Jacobson J, Dakhil SR, et al. Association of immune parameters with clinical outcome in stage III colon cancer: results of Southwest Oncology Group Protocol 9009. Cancer Immunol Immunother. 1999; 48:533–9. [PubMed: 10602891]
13. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol. 1993; 11(3):570–9. [PubMed: 8445433]
14. Stewart, AL.; Ware, JE. Measuring functioning and well being. Durham: Duke University Press; 1992. p. 102-42.
15. Meyer TJ, Mark MM. Effects of psychosocial interventions with adult cancer patients: A meta-analysis of randomized experiments. Health Psychol. 1995; 14:101–8. [PubMed: 7789344]
16. Walker LG. Hypnosis and cancer: host defenses, quality of life, and survival. Contemp Hypn. 1998; 15(1):34–8.
17. Richardson J, Smith JE, McCall G, et al. Hypnosis for nausea and vomiting in cancer chemotherapy: a systematic review of the research evidence. Eur J Cancer Care. 2007; 16:402–12.

18. Hall, M.; Lynn, SJ. Hypnotic treatment of women with breast or gynecological cancer. In: Hornyak Lynne, M.; Green Joseph, P., editors. Healing from within: the use of hypnosis in women's health care. Washington, DC, US: American Psychological Association; 2000. p. 139-60.

19. Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E. The effect of massage on cellular immunity, endocrine and psychological factors in women with breast cancer — a randomized controlled clinical trial. Auton Neurosci. 2008; 140:88–95. [PubMed: 18474451]

20. Ernst E. Massage therapy for cancer palliation and supportive care: a systematic review of randomized clinical trials. Support Care Cancer. 2009; 17:333–7. [PubMed: 19148685]

21. Heidt P. Effect of Therapeutic Touch on anxiety levels of hospitalized patients. Nurs Res. 1981; 30(1):32–7. [PubMed: 6906014]

22. Olson M, Sneed N, LaVia M, et al. Stress-induced immunosuppression and therapeutic touch. Altern Ther Health Med. 1997; 3(2):68–74. [PubMed: 9061991]

23. Post-White J, Kinney ME, Savik K, Gau JB, Wilcox C, Lerner I. Therapeutic massage and healing touch improve symptoms in cancer. Integr Cancer Ther. 2003; 2(4):332–44. [PubMed: 14713325]

24. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006; 5(354(1)):34–43. [PubMed: 16394300]

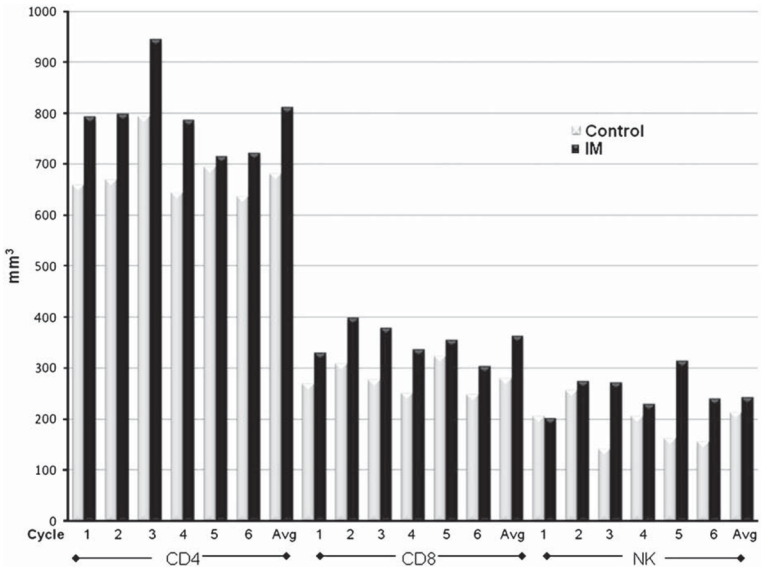

Fig. 1.
Immunologic profiles. Average for each cycle, Control vs IM.

Table 1

Descriptive statistics.

	IM (n=22)	Control (n=23)	*p* value
Age (years)			
Median	58	63.5	
Mean (range)	58.8 (30–82)	63.0 (47–83)	0.24
FIGO stage			
I	2	4	
II	2	1	
III	17	9	
IV	2	6	0.67
Grade			
Grade 1	2	4	
Grade 2	4	2	
Grade 3	17	14	
Median grade	3 (SD 0.65)	3 (SD 0.83)	0.51
CA 125 mean (U/ml)			
Initiation of therapy (range)	201 (9–1574)	204 (15–770)	0.97
Completion of therapy	22 (5–191)	18 (7–68)	0.50
Surgical cytoreductive status (residual disease at the completion of surgery)			
Optimal (<1 cm)	20	16	
Suboptimal (≥1 cm)	3	4	0.69

Table 2

Average MHI and FACT-O survey values.

	Group	Average value	*p* value
MHI			
Baseline	Control	194.6	0.62
	IM	190.8	
Cycle 3	Control	182.1	0.56
	IM	188.9	
Cycle 6	Control	196.2	0.96
	IM	196.7	
6 months	Control	203.2	0.18
	IM	186.6	
FACT-O			
Baseline	Control	143.2	0.39
	IM	152.1	
Cycle 3	Control	154.3	0.79
	IM	151.9	
Cycle 6	Control	157.9	0.60
	IM	152.0	
6 months	Control	173.2	0.43
	IM	162.1	