Radiation therapy in ovarian carcinoma

CARLOS F. DE OLIVEIRA, M.D.

Gynecologic Service, University Hospital of Coimbra, Coimbra

INTRODUCTION In many western countries, ovarian cancer is the most common cause of death in women with gynecological malignant tumors. Epithelial ovarian cancer accounts for 90% of all malignant ovarian tumors, and only 30% to 40% of these are limited to the pelvis at initial diagnosis (1). More than two-thirds of patients present disease involving the abdomino-pelvic cavity and 25% of the patients are found to have upper abdominal involvement after appropriate staging procedures (2). Ovarian cancer disseminates over serosal surfaces and remains confined to the abdomino-pelvic cavity for most of its natural history. This dissemination pattern presents a major problem in the management of this malignancy with radiation, because treatment of the entire peritoneal cavity is required to encompass the tumor volume. For patients with early ovarian cancer, the 5-year survival rates are low, ranging from 50% to 75% for stage I disease and 25% to 55% for stage II disease. One important reason for the low cure rates in this subgroup of patients is that many patients have occult metastases in other areas of the abdomen, such as diaphragm, paraaortic nodes, the omentum, and other pelvic and abdominal peritoneal surfaces (1).

Optimal cytoreductive surgery when possible, followed by cisplatin based chemotherapy remains the primary treatment for most of the patients diagnosed with epithelial ovarian carcinoma. Although these combination regimens have produced high clinical response rates in patients with stage III and IV disease, pathological complete response rates as documented by negative second-look laparotomy are only 30-40%. Another 20-50% of patients with a negative second-look laparotomy will eventually recur (3). Advances in cytoreductive surgery and postoperative chemotherapy, in the last decade, reached a plateau. In such circumstances we are faced with the need to take other therapeutic decisions.

RADIATION THERAPY The use of radiation therapy in the management of ovarian cancer continues to be a controversial subject. Controversy arises from several factors, including the early use of inappropriate techniques and doses of radiation and the selection on inappropriate patients such therapy (4). To be of curative benefit in ovarian cancer, radiation therapy must encompass the sites in which disease is most likely to recur postoperatively. Techniques that encompass the whole peritoneal cavity, rather than just the pelvis or lower abdomen alone, are likely to be most beneficial. The dose of radiation that can be safely delivered to this large volume is low in comparision to that considered necessary to eradicate most solid tumors. Thus, it is expected that abdominopelvic radiation therapy would benefit only patients in whom the volume of residual tumor remaining postoperatively in the upper abdomen is microscopic (4). Several possible mechanisms may help explain the failure of radiation therapy to control bulky residual disease, the first one being the relatively low dose of radiation that can be safely delivered, due to the limited tolerance of the bowel, kidney and liver. The second mechanism is the possible development of cross-resistance to radiation of the chemotherapeutically treated residual tumor (5).

In selecting patients with early stages disease who are appropriate for abdominopelvic radiation therapy, the amount and site of residual disease and the tumor grade are strong determinants of successful outcome. The *„Dembo prognostic model"* for epithelial ovarian cancer took into account these prognostic factors and defined three groups: a low-risk group, an intermediate-risk group and a high-risk group. This classification of patients is currently used in Toronto to select patients for radiation therapy and to understand their outcome after treatment *(Table 1.)* (4). According the *Toronto data* (4), patients in the low-risk category receive no additional therapy. Those in the

Table 1. „Dembo prognostic model" for epithelial ovarian cancer. Adapted from *Thomas and Dembo* (4)

LOW RISK:	Stage I, RD=0,Gr 1
INTERMEDIATED RISK:	Stage I, RD=0, Gr 2,3
	Stage II, RD=0, Gr 1, 2, 3
	Stage II, RD<2 cm, Gr 1,2
	Stage III, RD=0 or <2 cm, Gr 1
HIGH RISK:	Stage II, RD<2 cm, Gr 3
	Stage III, RD=0 or <2 cm, Gr 2,3

(RD = Residual disease; Gr = Grade)

Address correspondence to:

Carlos Freire de Oliveira, M.D.
Hospitais da Universidade de Coimbra
Sector de Ginecologia Oncologia
Coimbra, 3000 Portugal
Phone (351 39) 400500 Fax: (351 39) 721478

intermediate-risk category, in whom abdominopelvic radiation therapy is most appropriate as the sole postoperative treatment method, showed a 10-year disease-free survival of 67%. On the other hand patients in the high-risk category, receiving the same radiation therapy, presented only 20% 10-year disease-free survival.

RADIATION TECHNIQUE Several techniques delivering radiation to the entire peritoneal cavity have been developed. The two most commonly used are the moving-strip technique and the open field technique. In the *moving-strip technique* a small part of the abdomen is sequentially irradiated every day. The duration of the entire treatment course is approximately twice that of the open field and, theoretically, the prolonged treatment course might allow accelerated proliferation of tumor and possible reappearance of tumor metastases from the untreated area of the peritoneum back to the previously treated area (4). In *the open field technique* the whole volume is treated every day. *Dembo et al.* (6) compared these two techniques and the 5-year survival rates were indistinguishable between the two treatment arms and the acute toxicity was also similar.

According to *Thomas and Dembo* (4) „an optimal therapeutic ratio might be achieved with abdominopelvic irradiation if the following technical principles were followed:

1. The entire peritoneal cavity is encompassed using an open field technique.
2. No liver shielding is used, thus ensuring an adequate dose to the right hemidiaphragm.
3. The upper abdominal dose should not exceed 22.5-28 Gy in 100-120 cGy daily fractions.
4. Renal damage is avoided by partial kidney shielding, limiting the renal dose to 18-20 Gy.
5. The true pelvis is boosted to a total dose of 45 Gy in 180-220 cGy fractions.
6. Parallel opposing portals are used, with each field treated daily to minimize the dose per fraction employed. The beam energy must be sufficient to ensure a dose variation of less than or equal to 5%."

EARLY OVARIAN CANCER The early stages of the disease, which account for approximately 30% of yearly reported cases, represent theoretically the subset of ovarian cancer patients with better prognosis. Overall, patients with stage I disease have an excellent long-term prognosis, usually more than 80% 5-year relapse-free rates. Stages IA or IB tumors with poorly differentiated histology, stage IC as well as stage II disease represent unfavorable prognostic categories associated with high-risk of relapse in the abdominal cavity (4, 7). Frequent recurrences in the peritoneal cavity have led to various postoperative therapies. Among the several techniques the most often used are chemotherapy, external beam radiation therapy to the whole abdomen, or intraperitoneal installation of a radiocolloid.

RADIATION THERAPY VERSUS OBSERVATION In the *Princess Margaret Hospital* study (9) patients with stage Ia disease were randomized to receive postoperative pelvic radiation therapy or observation. There was no benefit in survival or prevention of relapses for patients receiving pelvic radiation. Abdominopelvic radiation therapy has not been the subject of a phase III trial in patients with stage Ia disease, although some studies have included a few of these patients.

RADIATION THERAPY VERSUS CHEMOTHERAPY Various studies have been made in an attempt to compare the relative effectiveness of abdominopelvic radiation therapy versus combination platinum-based chemotherapy in intermediate-risk patients. The randomized clinical trails were unable to be complete, possibly as a result of strong investigator bias or the widely divergent treatment methods. Patient accrual was difficult and the studies were closed before completion (4).

Thomas and Dembo (4) concluded that there are no firm data on which to base a preference for either radiation therapy or platinum-based combination chemotherapy for intermediate-risk patients.

Chiara et al. (7) conducted in Italy a randomized clinical trial comparing cisplatin plus cyclophosphamide versus whole abdominal radiotherapy in high-risk early-stage ovarian cancer patients. The study was prematuraly closed because 63% of all patients in the series were treated with chemotherapy. The 5-year survival was 71% and 53%, while relapse-free survival was 74% and 50% for chemotherapy and whole abdominal radiotherapy respectively. The differences were not statistically significant, but a short-term chemotherapy, including cisplatin, appears to be a safe treatment in comparison whole abdominal radiotherapy.

The *M.D. Anderson Hospital* randomized trial (8) involved stage I, II and III patients. Abdomino-pelvic radiation was compared with 12 cycles of melphalan. All patients had neither gross residual disease nor disease < 2 cm in diameter. No survival difference was detected with 5-year survival rates, which were 71% in one arm and 72% in the other.

RADIATION THERAPY VERSUS CHEMOTHERAPY AND RADIATION THERAPY The *Princess Margaret Hospital* (9) conducted a randomized trial comparing abdomino-pelvic radiation to pelvic radiation plus chlorambucil. The trial involved patients with stages Ib, II or III asymptomatic. The results didn't show any significant overall difference with a 5-year survival rate of 60% in the abdominal radiation arm versus 43% in the chlorambucil arm. However, when the analysis was confined to those who had a hysterectomy and bilateral salpingo-oophorectomy, the difference was significant ($p<0.02$), with a 5-year survival rate of 78% in the abdominal radiation arm versus 51% in the chlorambucil arm.

In the *National Cancer Institute of Canada Clinical Trials Group* (10) patients, with stages I, IIA „high-risk" ovarian car-

cinoma and IIB, IIIO (disease confined to the pelvis), were randomized either to abdominal radiotherapy, to melphalan or to intraperitoneal chromic phosphate (^{32}P). All patients were initially treated with pelvic radiotherapy. No significant difference was observed between the three arms. The 5-year survival was 62% in the abdominal radiotherapy arm, 61% in the melphalan arm, and 66% in the chromic phosphate arm. Concerning the disease-free survival melphalan had a marginally significantly superior disease-free survival experience compared with abdominal radiotherapy (p=0.015)

The *Danish Ovarian Cancer Group* (11) performed a randomized study of early epithelial ovarian cancer (stages Ib, Ic and II), comparing the adjuvant effect of whole abdominal radiotherapy with pelvic irradiation plus cyclophosphamide. Overall survival did not significantly differ between the two regimens. 4-year survival for patients treated with whole abdomen radiotherapy was 63% and 55% for patients treated with pelvic radiotherapy and cyclophosphamide. Recurrence-free survival was also equal for the two treatments. In this study the irradiation volume was exactly the same as in the Toronto trial, so the lack of difference cannot be explained by a too small irradiation volume.

ADVANCED OVARIAN CANCER

RADIATION THERAPY FOLLOWING SURGERY AND CHEMOTHERAPY Despite combined treatment approaches, the survival rates in advanced stage ovarian cancer have shown little improvement in the last decade.

The benefit of radiation therapy as an adjuvant to chemotherapy in advanced stage ovarian cancer has not been clearly defined. *Arian-Schad et al.* (5) reported a retrospective study concerning 20 patients with FIGO stage III epithelial ovarian cancer who had undergone maximum cytoreductive surgery and a combination platinum-based chemotherapy and were treated with irradiation to the abdomen and pelvis followed by a pelvis boost. The 3-year overall survival is correlated with the amount of residual disease. It was 100% for patients with no residual disease, 66.7% for ≤ 2 cm, and 26.7% for those with > 2 cm residual disease. This approach appeared to be most effective in patients with no visible disease after initial surgery.

Calkins et al. (12), from the Johns Hopkins Hospital, showed the results of a phase II study, in patients with stage III disease, using a new technique – the delayed split abdominal irradiation or DSA. This technique was designed to accomplish two goals: first, to enable treatment of the entire peritoneal cavity and the pelvis on a single treatment day without undue acute morbidity and second, to deliver an adequate tumoricidal fractional dose of radiation, 1.5 Gy to the upper abdomen and 2 Gy to the pelvis. This was accomplished by dividing the abdomen into upper and lower halves treating the two fields separately with at least 6 hrs between fractions. The survival advantage from this study is difficult to determine in a non-randomized review, but the DSA irradiation is an acceptable technique for delivering a high fractional dose of radiation to the entire peritoneal cavity.

In a pilot study *King et al.* (13) assessed the feasibility of concomitant whole abdominal irradiation and intraperitoneal cisplatin chemotherapy in patients with advanced ovarian cancer. They concluded that this combination of radiotherapy and intraperitoneal chemotherapy confers no therapeutic advantage on patient with large residual disease and is more toxic than standard chemotherapy or radiation therapy regimens alone.

Other reported series have included patients with different surgical and chemotherapy treatments and varied criteria for evaluation of response. Moreover range of radiation techniques and dose have been employed. This lack of uniformity including the different sequences of therapeutic modalities applied contributes to the variations in treatment results. Prospective randomized trials comparing post-surgical use of chemotherapy alone with chemotherapy plus radiation are still lacking.

RADIATION THERAPY AFTER SECOND-LOOK LAPAROTOMY A second laparotomy is performed after completion of chemotherapy that usually requires 6 to 8 months. The merits of second-look laparotomies and further therapy are debatable. Some authors believe that the lack of acceptable treatment alternatives for patients with positive findings eliminates the need for this procedure. Second-look laparotomies in patients who are clinically free of disease are pathologically negative in 25% to 49% of cases (14). Recurrence rates after negative second-look laparotomies in ovarian cancer patients range from 5.9% to 50% (14). Therefore, it is believed that further consolidative therapy is needed in patients with negative second-look laparotomies.

Menczer et al. (15) from Israel, compared the outcome in two non-randomized groups of ovarian cancer patients in complete clinical remission who had minimal or no residual disease at second-look laparotomy. One group was treated after the reexploration with cisplatin intraperitoneal chemotherapy, the other one with abdominopelvic irradiation. The data of this study seem to suggest that the survival and the progression free interval duration of patients in complete clinical remission, who, subsequent to second-look laparotomy, were treated with intraperitoneal cisplatin chemotherapy are better than the ones of such patients treated by abdominopelvic irradiation. This difference was statistically significant only in patients with a negative second-look laparotomy.

In a *California phase II study* (16) the authors evaluated the role of whole-abdominal radiotherapy for patients with minimal residual tumor documented at laparotomy following initial surgery and adjunctive cisplatin-based chemotherapy. The results of this study were discouraging. Despite completion of the planned course of radiotherapy in 14 of the 16 treated patients, the overall median progression-free interval was only

9 months. Survival after documentation of progression was short.

The *Swiss Group for Clinical Cancer Research* (SAKK) decided in 1985 to study the feasibility and efficacy of whole abdominal irradiation after short-course chemotherapy (17). Their aims were to induce a high number of pathologically verified complete remissions with surgery plus 4 cycles of cisplatin and melphalan and to prevent relapse with whole abdominal irradiation in a target population of patients in remission. The study concluded that whole abdominal irradiation as a consolidation treatment can neither prevent relapse in patients with pathological or clinical complete response, nor be used as an efficient salvage treatment for patients with microscopic residual disease after melphalan and cisplatin. The whole abdominal irradiation was hardly feasible as a consolidation treatment for the majority of the patients in remission, even after a short-course chemotherapy.

Two randomized trials, published recently, try to clarify the role of the whole abdominal radiation after second-look in ovarian cancer patients responding to surgery and chemotherapy. The Italian group (18) presents the results of a randomized study in which advanced ovarian cancer patients with pathologically confirmed complete response or with minimal residual disease after second-look (<2 cm) were treated with whole abdominopelvic radiotherapy or with three additional courses of the same chemotherapy that induce the response. With a median follow-up of 22 months the analysis of the results shows: the disease progression was observed in 11 of 20 patients (55%) treated with radiotherapy and in 6 of 21 patients (28.5%) treated with chemotherapy (p=0.08); the disease-related deaths occurred in 9 patients in the radiotherapy arm (45%) and in 3 patients (14.2%) in the chemotherapy arm (p=0.02). In conclusion the chemotherapy was more effective than radiotherapy in controlling disease progression after surgery and front-line chemotherapy in patients with no or minimal residual disease at second-look.

The second trial comes from the *North Thames Ovary Group Study* (19) with the aim of determining, in a randomized trial of advanced ovarian carcinoma, whether consolidation therapy with whole abdominal radiotherapy after chemotherapy improves survival and disease-free survival compared with the same continued chemotherapy (5 courses of carboplatin). All patients received, before response evaluation, and after initial surgery, five monthly courses of carboplatin. The data reported don't show any significant difference between both groups, concerning overall survival or progression-free survival. There was also no difference in survival among patients in whom no residual disease was found at second-look.

SALVAGE RADIATION THERAPY Patients with advanced and recurrent ovarian carcinoma continue to pose a therapeutic challenge and demonstrate a need for evaluating alternative treatment modalities to improve on the existing low survival rates.

To evaluate the role of whole abdomen radiation therapy with a pelvic boost as a salvage therapeutic modality, *Reddy et al.* (3) treated patients with ovarian carcinoma who had failed initial systemic chemotherapy. The 4-year actuarial survival and recurrence-free survival rates for the entire group of 44 patients were 23% and 22% respectively. The survival and the recurrence-free survival rates for the group with microscopic residual disease at 37% and 42% were significantly better than those for patients with macroscopic residual disease at 9% and 5%, respectively. The whole abdomen radiation therapy with a pelvic boost is feasible as a salvage therapeutic modality with minimal acute and late toxicity. The data suggest that this method of treatment is effective in management of patients with minimal residual disease (20).

In another study from the *Fox Chase Cancer Center,* in Pennsylvania (21), 33 patients with recurrent ovarian cancer were irradiated to 47 sites (pelvis, abdomen, chest, brain, etc.). Abdominopelvic fields were not designed to cover the whole abdomen but were tailored to include the gross tumor volume with additional margin to irradiate the planning target volume adequately. For the entire group, the complete symptomatic response was 51%, and the overall symptomatic response was 70%. This is the first published analysis to evaluate the palliative efficacy of radiotherapy rigorously among a group of patients whose initial care included agressive debulking surgery and cisplatin based chemotherapy. The analysis concluded that durable palliation can be achieved with radiotherapy in most patients with recurrent ovarian cancer.

RADIATION THERAPY TOXICITY

ACUTE TOXICITY According to the *Princess Margaret Hospital* (9) study the acute toxicity was similar in both techniques of whole abdomen irradiation – moving-strip and open field. Fatigue, which increases as treatment progresses, is the most common complaint. Anorexia, meteorism, mild diarrhea and nauseas are very common. Vomiting is occasional and, in general, hematologic toxicity is mild (4). Treatment interruption for acute toxic effects is rare, if radiation therapy is the sole post-operative therapy. Acute symptoms tend to disappear within a few weeks of treatment completion.

LATE TOXICITY Pneumonitis or lung fibrosis and gastrointestinal damage, consisting of bloating or intermittent diarrhea related to particular foods, occur in 5-20% of patients (4). Approxi-

Table 2. Summary of late bowel complications after abdominopelvic irradiation

Serious complication rates:	
Low dose (2250 rad/22 fractions)	1.4%
High dose (3000 rad/8 fractions)	14.3%
Bowel surgery	5.6%
Deaths	0.4%

(adapted from Thomas and Dembo (4)

mately 50% of patients have elevated alkaline phosphatase levels transiently, but clinical evidence of liver damage is rare (4). *Table 2.* adapted from *Thomas and Dembo* (4), summarizes the major bowel complications from 1098 patients in 10 series.

The frequency of serious gastrointestinal morbidity and its severity appears to be related to the total dose of radiation, the dose per fraction, and the extend of previous surgery, particularly lymph node sampling (4).

RADIOACTIVE ISOTOPES Colloids labelled with radioactive isotopes of phosphorus or gold have been used. ^{32}P is the most attractive isotope, given that is a pure beta emitter. Despite the intuitive appeal of the use of intraperitoneal ^{32}P, a therapeutic value has not been established for this therapy.

Epenetos at al. (22, 23) since 1983 have been investigating the possibility of tumor targeting and therapy by the intraperitoneal administration of radiolabelled monoclonal antibodies in patients with ovarian cancer. They treated a group of 52 ovarian cancer patients with yttrium-90-labelled monoclonal antibody HMFG1 administered intraperitoneally following conventional surgery and chemotherapy. The treatment was well tolerated and this study suggests that patients with advanced ovarian cancer who achieve a complete remission following conventional therapy may benefit from further treatment with intraperitoneal radioactive monoclonal antibody.

INTRAPERITONEAL ^{32}P IN EARLY STAGE As it was said before the *NCI Canada* trial (10), comparing adjuvant treatment with abdominal radiotherapy, melphalan or intraperitoneal ^{32}P did not show any difference concerning survival between the three arms.

A randomized trial comparing cisplatin (50 mg/m2 – six courses) with intraperitoneal ^{32}P or whole abdomen irradiation as adjuvant treatment of ovarian cancer patients (FIGO stages I to III disease without residual disease after laparotomy) was accomplished by the *Norwegian Radium Hospital* (1). Patients randomized to received ^{32}P with extensive intraperitoneal adhesions were treated with whole abdominal irradiation instead of ^{32}P. Crude and disease-free survival were similar in both groups. Late bowel complications occurred more often in patients treated with ^{32}P compared with the cisplatin group. Because of this high number of late bowel complications after ^{32}P the authors recommended that cisplatin must be used as standard adjuvant treatment for subsquent controlled studies.

Considering the short penetrating power of ^{32}P, the dose to the retroperitoneal nodes is negligible, and the radiation dose distribution over the peritoneum is often variable and unpredictable. *Soper et al.* (24) treated 49 women with apparent stage I and II ovarian cancer with intraperitoneal ^{32}P and confirm that their experience shows the failure of adjuvant ^{32}P as adjuvant therapy to prevent extraperitoneal recurrences in women with apparent early-stage ovarian carcinoma who have undergone only casual surgical staging procedures. For this reason ^{32}P is not appropriate therapy for this kind of patients.

INTRAPERITONEAL ^{32}P AT SECOND-LOOK LAPAROTOMY In the *Norwegian Radium Hospital study* (25) 50 patients with negative second-look findings were assigned randomly to receive intraperitoneal ^{32}P or no treatment and the results of the log-rank test for differences in survival distributions between the two groups were not significant or even suggestive of a prolonged survival in the ^{32}P arm.

Two other non-randomized studies (14, 26) treating patients without evidence of disease at second-look laparotomy with ^{32}P concluded that postsecond-look intraperitoneal ^{32}P treatment improved the progression-free survival and possibly overall survival rates.

REFERENCES

1. Vergote IB, Vergote-De Vos LN, Abeler VM, et al. Randomized trial comparing cisplatin with radioactive phosphorus or wholeabdomen irradiation as adjuvant treatment of ovarian cancer. Cancer 1992; 69:741-749.

2. Piver MS, Barlow JJ, Lele SB. Incidence of subclinical metastasis in stage I and II ovarian carcinoma. obstet. Gynecol, 1978; 52:100-104.

3.Reddy S, Lee MS, Yordan E, et al. Salvage whole abdomen radiation therapy: its role in ovarian cancer. Int J Radiat Oncol Biol Phys 1993; 27:879-884.

4. Thomas GM, Dembo AJ. Integrating radiation therapy into management of ovarian cancer. Cancer 1993; 71:1710-1718.

5 Arian-Schad KS, Kapp DS, Hackl A, et al. Radiation therapy in stage III ovarian cancer foliowing surgery and chemotherapy: prognostic factors, patterns of relapse, and toxicity: a preliminary report. Gynecol Oncol 1990; 39:47-55.

6. Dembo AJ, Bush RS, Beale FA, et al. A randomized clinical trial of moving strip versus open field whole abdominal irradiation in patients with invasive epithelial ovarian cancer. Int J Radiat Oncol Biol Phys 1983; 9:97-99.

7. Chiara S, Conte PF, Franzone P, et al. High-risk early-stage ovarian cancer. Randomized clinical trial comparing cisplatin plus cyclophosphamide versus whole abdominal radiotherapy. Am J Clin Oncol 1994; 17:72-76.

8. Smith JP, Rutledge FN, Delclos L. Postoperative treatment of early cancer of the ovary: a randomized trial between postoperative irradiation and chemotherapy. NCI Monogr 1975; 42:149-153.

9. Dembo AJ, Bush RS, Beale FA, et al. Ovarian carcinoma: improved survival following abdominopelvic irradiation in patients with complete pelvic operation. Am J Obstet Gynecol 1979; 134:793-800.

10. Klaassen D, Shelley W, Starreveld A, et al. Early stage ovarian cancer: a randomized clinical trial comparing whole abdominal radiotherapy, melphalan, and intraperitoneal chromic phosphate. A National Cancer Institute of Canada Clinical Trials Group report. J Clin Oncol 1988; 6:1254-1363.

11. Sell A, Bertelsen K, Andersen JE, et al. Randomized study of whole-abdomen irradiation versus pelvic irradiation plus cyclophosphamide in treatment of early ovarian cancer. Gynecol Oncol 1990; 37:367-373.

12. Calkins AR, Rosenheim NB, Fox MG, et al. Delayed split whole abdominal irradiation in the combined modality treatment of ovarian cancer. Int J Radiat Oncol Biol Phys 1991; 20:661-665.

13. King LA, Downey GO, Potish RA, et al. Concomitant whole-abdominal radiation and intraperitoenal chemotherapy in advanced ovarian cancer. A pilot study. Cancer 1991; 67:2867-2871.

14. Spencer TR, Markes Jr RD, Fenn JO, et al. Intraperitoneal P-32 after negative second-look laparotomy in ovarian cancer. Cancer 1989; 63:2434-2437.

15. Menczer J, Ben-Baruch G, Modan M, et al. Intraperitoneal cisplatin chemo-

therapy versus abdominopelvic irradiation in ovarian carcinoma patients after second-look laparotomy. Cancer 1989; 63:1509-1513.

16. Kucera PR, Berman ML, Treadwell P, et al. Whole-abdominal radiotherapy for patients with minimal residual epithelial ovarian cancer. Gynecol Oncol 1990; 36:338-342.

17. Buser K, Bacchi M, Goldhirsch A, et al. Treatment of ovarian cancer with surgery, short-course chemotherapy and whole abdominal radiation. Ann Oncol 1996; 7:65-70.

18. Bruzzone M, Repetto L, Chiara S, et al. Chemotherapy versus radiotherapy in the management of ovarian cancer patients with pathological complete response or minimal residual disease at second-look. Gyencol Oncol 1990; 38:392-395.

19. Lambert HE, Rustin GJS, Gregory WM, et al. A randomized trial comparing single-agent carboplatin with carboplatin followed by radiotherapy for advanced ovarian cancer: a North Thames Ovary Group Study. J Clin Oncol 1993; 11:440-448.

20. Reddy S, Hartsell W, Graham J, et al. Whole-abdomen radiation therapy in ovarian carcinoma: its role as a salvage therapeutic modality. Gynecol Oncol 1989; 35:307-313.

21. Corn BW, Lanciano RM, Boente M, et al. Recurrent ovarian cancer. Effective radiotherapeutic palliation after chemotherapy failure. Cancer 1994; 74:2979-2983.

22. Epenetos AA, Courtenay-Luck N, Halnan KE, et al. Antibody guided irradiation of malignant lesions: three cases illustrating a new method of treatment. Lancet 1984; 1:1441-1443.

23. Hird V, Maraveyas A, Snook D, et al. Adjuvant therapy of ovarian cancer with radioactive monoclonal antibody. Br J Cancer 1993; 68:403-406.

24. Soper JT, Berchuck A, Clarke-Pearson DL. Adjuvant intraperitoneal chromic phosphate therapy for women with apparent early ovarian carcinoma who have not undergone comprehensive surgical staging. Cancer 1991; 68: 725-729.

25. Vergote IB, Winderen M, De Vos LN, et al. Intraperitoneal radioactive phosphorus therapy in ovarian carcinoma. Analysis of 313 patients treated primarily or at second-look laparotomy. Cancer 1993;71:2250-2260.

26. Varia M, Rosenman J, Venkatraman S, et al. Intraperitoneal chromic phosphate therapy after second-look laparotomy for ovarian cancer. Cancer 1988; 61:919-927.