Adjuvant treatment of early stage ovarian carcinoma

A. GADDUCCI (*) - B. DEL BRAVO (*) - A. CARDOSI CARRARA (*)
M. D'AMICO (*) - P. FIORETTI (*)

Summary: Surgery is considered the mainstay of diagnosis and treatment in early ovarian carcinoma. Only accurate staging laparotomy can detect subclinical metastases remote from the ovary, thus allowing the identification of the truly early tumors. However the complete macroscopic removal of neoplastic disease is not synonymous with cure. Many postoperative treatments have been carried out in order to improve the prognosis of patients with stage I-II ovarian carcinoma. The present paper reviews the main clinical trials on the employment of external radiotherapy, intraperitoneal radioisotope instillation and systemic chemotherapy in the management of early ovarian carcinoma. The patients appear to benefit from adjuvant treatment, with the exception of those with stage IAi-IBi well differentiated tumor, even if there is no agreement in literature about the superiority of a particular therapeutic approach. However the high response rates obtained in patients with advanced ovarian carcinoma with DDP containing combination chemotherapy have suggested to clinicians the use of such treatment also in early stage tumors. In our experience none of the 11 stage I ovarian cancer patients, who received 6 courses of DDP-based combination chemotherapy, have developed recurrent disease after a median follow-up of 54 months (with a range from 24 to 72 months).

Key words: early ovarian carcinoma; surgery; radiotherapy; chemotherapy.

INTRODUCTION

It is well known that only one fourth of cases of ovarian carcinoma are diagnosed in early (FIGO I and II) stages of disease.

An accurate surgical staging is necessary to detect microscopic metastatic disease remote from the ovary, thus allowing the identification of the truly early tumors. The staging laparotomy must include ascitic fluid sampling or peritoneal washing from the paracolic gutters and cul de sac, and a careful visual and manual inspection of diaphragm, liver and bowel, followed by total hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, appendicectomy, multiple peritoneal biopsies and sampling of paraaortic and pelvic lymphnodes ([1, 2]).

In 1978 Piver *et al.* ([3]) described the incidence of subclinical metastases in 36 patients with presumed stage I-II ovarian carcinoma undergoing laparoscopy (31 patients) or restaging laparotomy (5 patients) before any further treatment. In this series, 11.3% of 27 patients with stage I ovarian carcinoma had diaphragmatic metastases, 10.3% had para-aortic lymphnode metastases, 8.1% had pelvic lymphnode metastases, 3.2% had omental metastases and 32.9% had positive peri-

(*) Department of Gynecology and Obstetrics, University of Pisa (Italy)

toneal cytologic washing: of the 9 patients with stage II disease, 23% had diaphragmatic metastases, 10% had paraaortic lymphnode metastases, 0% had omental metastases and 12.5% had positive peritoneal washing.

The Ovarian Cancer Study Group (OCSG), including the Mayo Clinic, MD Anderson Tumor Hospital, Roswell Park Memorial Institute and the National Cancer Institute, performed a systemic restaging study on 100 patients referred to one of these institutions with stage I or II ovarian carcinoma [4]. The restaging laparotomy showed a more advanced neoplasia in 31 patients; in particular 23 of these 31 subjects (77%) were found to have a stage III tumor.

In addition to an exact definition of the spread of the tumor, an optimal surgery is an essential prerequisite for a long disease free survival also in patients with localized ovarian carcinoma [5]. However the complete macroscopic removal of all tumor in early ovarian carcinoma is not synonymous with cure: in fact 30-40% stage I and 60% stage II patients can be expected to relapse within 5 years [6, 7, 8, 9].

Several studies have been performed in order to verify the effectiveness of some forms of postoperative treatment in patients with early ovarian carcinoma. The great variability of survival rates reported in literature depends on both different and sometimes suboptimal staging procedures and different distribution of prognostic factors in the groups of examined patients.

The aim of this paper is to review the most important clinical trials on the use of external radiotherapy, intraperitoneal radioisotope administration and systemic chemotherapy in the treatment of early stage ovarian carcinoma.

RADIOTHERAPY

From 1960 to 1970-75, pelvic radiotherapy was the most used postoperative treatment in patients with stage I-II ovarian carcinoma. Fuks [10], who reviewed the literature of that period, reported 5-year survival rates of 70% and 58% respectively in 389 stage I patients treated by bilateral salpingo-oophorectomy with hysterectomy, and in 707 stage I patients who underwent bilateral salpingo-oophorectomy with hysterectomy followed by pelvic radiotherapy: the same Author referred 5-year survival rates of 21% and 32% respectively in 103 stage II patients treated with surgery alone and in 693 stage II patients treated with surgery and radiotherapy.

Terada *et al.* [11] treated 34 stage II ovarian carcinoma patients with pelvic radiotherapy at the dose of 5000 cGy. In this series the 5-year actuarial disease-free survival rate was 53%. In a randomized study on 54 patients with stage IA ovarian carcinoma, Dembo *et al.* [12] observed 4/27 (14.8%) recurrences among patients who had no further postsurgical treatment and 5/27 (18.5%) recurrences among those who received 4500 cGy pelvic irradiation.

The United States Gynecologic Oncologis Group (US GOG) randomized 168 patients with stage I ovarian carcinoma undergoing total abdominal hysterectomy with bilateral salpingo-oophorectomy in 3 arms: the first had no further treatment, the recond received 5000 cGy pelvic radiotherapy and the third received monochemotherapy with melphalan (L-PAM) (0.2 mg/kg/day orally for 5 days every 4 weeks for 18 months) [13]. Only 86 (48%) patients were available for evaluation. Relapsing disease occurred in 2/34 (6%) patients of L-PAM arm; this recurrence rate was significantly lower than that of the radiotherapy arm (7/23, 30%) and control arm (5/29, 17%) ($p<0.05$). In particular, an extrapelvic relapse was observed in 3% of patients treated with chemotherapy, in 14% of those who received no postsurgical thera-

py and 26% of those treated with radiotherapy. Therefore these Authors concluded that in patients with stage I ovarian carcinoma, the adjuvant administration of L-PAM seemed to give a better clinical outcome with respect to pelvic radiotherapy or no further treatment. These conclusions were not accepted by Dembo *et al.* [14], because the 3 treatment arms were not equally matched by patient numbers or prognostic variables. Furthermore, these Authors criticized the handling of the statistical data by the US GOG. In fact, using the two- sided Fisher exact test, there was no significant difference in overall recurrence rate and in extrapelvic recurrence rate between L-PAM arm and control arm ($p=0.30$ and $p=0.26$ respectively), or between radiotherapy arm and control arm ($p=0.43$ and $p=0.44$ respectively).

According to Dembo *et al* [14], the lower incidence of overall relapses and extrapelvic relapses between L-PAM arm and radiotherapy arm ($p=0.034$ and $p=0.028$ respectively) was due to a thwarted randomization that caused great differences in the distribution of prognostic factors between the 2 arms.

Dembo *et al.* [15, 16] randomized 190 patients with ovarian carcinoma in stage IB (18 patients), stage II (132 patients) and asymptomatic stage III (40 patients) in an arm treated with pelvic radiotherapy (4500 cGy in 20 fractions), an arm treated with pelvic radiotherapy plus chlorambucil (CBL) (6 mg/day for 2 years) and an arm treated with abdominopelvic radiotherapy (2250 cGy on the pelvis in 10 fractions followed by a moving strip irradiation on the abdomen and pelvis, delivering a dose of 2250 cGy in 10 fractions). Stage III patients were randomized only between the last 2 arms. The 10 year survival rate was better in patients who received abdomino-pelvic radiotherapy with respect to those treated with pelvic radiotherapy plus CBL (46% vs 31%, $p<0.05$). The survival advantage was observed only in patients who had undergone bilateral salpingo-oophorectomy with total hysterectomy (64% vs 40%, $p<0.007$), but not in those who had received less extensive surgery (12% vs 10% $p=0.23$). The better clinical outcome in patients treated with complete surgery and abdomino-pelvic radiotherapy was due to a decrease in abdominal recurrences.

Subsequently Dembo *et al.* [17] performed a randomized study in order to compare the moving strip technique (2250 cGy in 10 fractions on the abdomen plus 2250 cGy pelvic boost in 10 fractions) with the open field technique (2250 cGy on the whole abdomen in 22 fractions plus 2250 cGy pelvic boost in 10 fractions) in 166 patients with stage Ib, II and asymptomatic III ovarian carcinoma. The moving strip technique, which irradiates small segments over a shorter period of time, can deliver a biologically higher dose than the other. Five-year survival rate was 44% in the moving strip arm and 45% in the open field arm.

The acute toxicity was similar in both groups, while severe late complications requiring bowel surgery occurred in 6.1% of patients treated with the moving strip technique and in 1.2% of those treated with open field technique. Therefore this latter seemed to be preferred, since it was associated with a reduced toxicity with respect to the former one.

On the basis of an accurate multivariate analysis of prognostic factors in ovarian carcinoma patients treated at the Princess Margaret Hospital, Dembo [18, 19, 20] subdivided the patients with stage I, II and III with no or small residual disease in 3 groups according to stage, residuum and histologic features (low, intermediate and high risk group). The low risk group included patients with stage I well differentiated neoplasia, with a 5-year survival rate of 95% after surgery alone; the inter-

mediate risk and the high risk groups had a 5-year survival rate of 70% and 30% respectively after surgery plus abdominopelvic radiotherapy. Therefore, according to Dembo, low risk patients needed no further treatment after surgery, while intermediate risk patients and high risk patients needed abdomino-pelvic radiotherapy and a combined modality approach (6 courses of chemotherapy with cisplatin (DDP) containing regimens followed by abdominopelvic radiotherapy) respectively.

Leers and Kock ([21]) retrospectively evaluated 127 patients with stage I, II and III ovarian carcinoma with no or small residual disease treated with abdominopelvic radiotherapy from 1971 to 1984. These Authors used the moving strip technique (2250-2750 cGy on the abdomen in 8 fractions plus 2000 cGy pelvic boost in 10 fractions) until 1982 and the open field technique (2500 cGy on the abdomen in 25 fractions plus 2250 pelvic boost in 10 fractions) later. The 5-year actuarial survival rate was 71% and the disease-free survival rate was 64%. In particular the 5-year actuarial survival rates were 71%, 84% and 63% for stage I, II and III respectively, and the disease-free survival rates were 64%, 70% and 41% respectively. The 5-year actuarial survival rate was 78% in completely staged patients and 61% in incompletely staged ones. These Authors concluded that radiotherapy could represent a good treatment in patients with early stage ovarian carcinoma.

Piver *et al.* ([22]) reported the experience of the Roswell Park Memorial Institute in 31 patients with stage II ovarian carcinoma. Sixteen patients received 3000 cGy whole abdominal irradiation with open field technique in 30 fractions, followed by 2000 cGy pelvic boost in 10 fractions; while 15 patients received 4000-5000 cGy pelvic irradiation in 20-25 fractions followed by the administration of L-PAM at the dose of 0.2 mg/kg day orally for 5 days every 4 weeks for 12 months. The neoplasia relapsed in 13/16 (81%) patients of the first group and in 6/15 (40%) patients of the second group. The 5-year survival rates were 40% and 50% respectively. None of the two modalities of treatment seemed to increase patients' survival with respect to surgery alone. It is remarkable to remember that the radiotherapy dose delivered to ovarian carcinoma patients has not been established upon data obtained from dose-response curves or from analysis of recurrences for different dose levels, but it has been empirically fixed on the basis of the tolerance of normal tissues to irradiation. The radiation dose-tumor volume relationship has been studied in squamous cell carcinoma of the head and neck. For this neoplasia, 3000 cGy and 5000 cGy irradiation is respectively needed to obtain a 50% and 90% of local control of subclinical disease. To reach the same control rates, 5000 cGy and 6000 cGy are required with macroscopic lesions up 2 cm, and 6000 cGy and 7000 cGy are needed with 2-4 cm lesions. These data cannot be directly extrapolated from squamous cell carcinoma of the neck and head to the ovarian adenocarcinoma. Notwithstanding, in Piver's series the high recurrence rate after abdominopelvic radiotherapy seemed to show that 3000 cGy dose to the abdomen often failed to produce a tumoricidal effect on subclinical metastasis of ovarian carcinoma.

Another clinical study of the Roswell Park Memorial Institute evaluated the effectiveness of intraperitoneal administration of chromic phosphate (P32) in 25 patients with stage I ovarian carcinoma after total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without omentectomy ([23]).

The 10 year disease-free survival rate was 75%. These data did not show any significant advantage of adjuvant P32 treatment.

Near the M. D. Anderson Hospital, Smith *et al.* [24] carried out a randomized clinical trial in order to compare abdominopelvic radiotherapy by moving-strip technique (2600-2800 cGy on the abdomen in 8 fractions plus 2000 cGy pelvic boost in 10 fractions) with a monochemotherapy with L-PAM (0.2 mg/kg/die orally for 5 days every 4 weeks for 12 months) in patients with stage I, stage II and minimal residual stage III ovarian carcinoma. The 5- year survival rate was 71% in the 70 patients of radiotherapy arm, and 72% in the 79 patients of L-PAM arm. Ten per cent of the irradiated patients developed severe bowel complications requiring surgery. Since the survival curves were similar with both treatments, and chemotherapy was associated with less toxicity, these Authors suggested that L-PAM administration should be preferred as postoperative therapy in patients with early stage ovarian carcinoma. However this conclusion was criticized by Dembo [18, 25], since the two treatment arms were not balanced for prognostic factors. Moreover, the technique utilized at the M. D. Anderson Hospital differed from that employed at the Princess Margaret Hospital for the use of shorter fields and liver shielding, so providing possible sanctuary sites for neoplastic recurrence.

CHEMOTHERAPY

Several other studies on the role of chemotherapy in the treatment of early stage ovarian carcinoma have been subsequently performed.

After complete surgery and postoperative radiotherapy, 301 patients with stage I-II ovarian carcinoma were randomized by Davy *et al.* [26] to receive a monochemotherapy with thiotepa (60 mg i.m. every 2 weeks for twice followed by 15 mg biweekly for six months) or no further treatment. The postoperative irradiation consisted in isotope instillation or, if there were extensive postoperative adhesions, in 4000 cGy pelvic radiotherapy in 20 fractions. After an average follow-up of 59.6 months, a recurrent disease was observed in 38/151 (25%) patients who received thiotepa and in 37/150 (24.6%) patients who had not received this drug.

Therefore the adjuvant administration of thiotepa offered no additional benefit.

The Clinical Trials Group of the National Cancer Institute of Canada [27] planned a randomized study for patients with high risk early stage ovarian carcinoma, after total abdominal hysterectomy and bilateral salpingo-oophorectomy. Patients were randomized to either pelvic radiotherapy (2250 cGy in 10 fractions) followed by abdominal irradiation (2250 cGy on the whole peritoneal cavity in 20 fractions by open field technique or in 10 fractions by moving strip technique) (107 patients), or pelvic radiotherapy (4500 cGy in 20 fractions) followed by administration of L-PAM (8 mg/mq/day orally for 4 days every 4 weeks for 18 months) (106 patients), or pelvic radiotherapy (4500 cGy in 20 fractions) followed by intraperitoneal administration of P32 (10-20 uC) (44 patients). Entry of patients to the third arm was closed early because of a high incidence of severe late toxicity. The 5-year survival rate was 62% in the abdominal radiotherapy arms, 61% in the L-PAM arm, and 66% in the P32 arm, without any significant difference. Four (3.7% patients of L-PAM arm developed a myelodysplastic syndrome or an acute leukemia, while 12 (11.2%) patients of abdominal radiotherapy arm experienced a bowel obstruction requiring surgery.

Forty-six patients with stage I-II ovarian carcinoma were treated by Mackintosh *et al.* [28] with a monochemotherapy with cyclophosphamide (CTX) 1 g/mq i.v. every 3 weeks for 10 courses) (36 patients) or L-PAM (0.2 mg/kg/day orally

for 5 days every 6 weeks for 12 courses) (8 patients). The 5-year actuarial disease-free survival rate was 48% on the whole series, 89% in patients with stage IA and IB carcinoma and 24% in patients with stage IC and II tumor. In this latter subset, the administration of a monochemotherapy with an alkylant agent did not improve patients survival with respect to surgery alone.

In 1976 the OCSG planned 2 randomized clinical trials in patients with surgically staged early ovarian carcinoma ([29, 30]).

In 1978 the US GOG joined these studies ([29, 30]).

The first trial included 81 patients with stage IAi-IBi, G1-G2 tumor, who were randomly assigned to either monochemotherapy with L-PAM (0.2 mg/kg/day orally for 5 days every 4 to 6 weeks for 12 courses) or no adjuvant treatment. The 5-year survival rate was greater than 90% in both arms, which were well matched for the common prognostic factors. No second neoplasia occurred in patients treated with L-PAM. Only 1/35 (2.8%) asymptomatic patients, who underwent a second-look surgery, had persistent disease. According to these data, patients with stage IAi-IBi, G1-G2 ovarian carcinoma needed neither postoperative treatment nor second-look surgery.

The second study included 148 patients with stage IAii-IBii-IC-II ovarian carcinoma or with stage IAi-IBi G3 tumor. They were randomized to receive L-PAM (0.2 mg/kg day orally for 5 days every 4 to 6 weeks for 12 courses) or intraperitoneal P32 (15uC).

The 5-year disease-free survival rate was about 80% in both groups of patients, which were well balanced for the common prognostic factors. These data seemed to show that there was no significant difference in the therapeutic effectiveness of these two modalities of treatment.

Fiorentino *et al.* ([5]) examined 37 patients with early ovarian carcinoma, who underwent 5 courses of postoperative chemotherapy with Adriamycin (ADM) (55 mg/mq i.v. day 1) plus CTX (1200 mg/mq i.v. day 1) every 3 weeks. Sixteen patients had had a complete first line surgery. In the other 21 patients some of the surgical procedures required for an accurate staging had been omitted during the first operation, and a completion of staging was attempted through laparoscopy including peritoneal cytology and random biopsies; moreover during the second look laparotomy, performed after the fifth course of chemotherapy, the first line surgery was completed by the removal of the residual organs.

Recurrent disease was observed only in patients undergoing limited initial surgery. The 5-year actuarial disease free survival rate was 100% in patients with complete first surgery and 40% in those with suboptimal first surgery.

Since combination chemotherapy including DDP represents the most effective treatment in advanced ovarian carcinoma, such treatment has been recently proposed also in patients with early tumor ([3, 31, 32, 33]). In particular the US GOG has opened a clinical trial in order to compare a short term combination chemotherapy including DDP (100 mg/mq i.v. day 1) plus CTX (1000 mg/mq i.v. day 1) every 21-35 days for 3 courses with intraperitoneal P32 in patients with stage II or poor prognosis stage I ovarian carcinoma ([30]).

The Italian Inter-regional Cooperative Group of Gynecologic Oncology designed a randomized clinical trial for stage I ovarian carcinoma, including 3 different protocols ([34]).

After complete surgical staging, patients with stage IAi or IBi, G1 tumor had no adjuvant treatment (Protocol A); patients with stage IAi or IBi, G2-G3 tumor were randomized to either no adjuvant treatment or DDP (50 mg/mq i.v. every 4

weeks for 6 courses) (Protocol B); patients with stage IAii, IBii or IC were randomly assigned to receive DDP (50 mg/mq i.v. every 4 weeks for 6 courses) or intraperitoneal P32 (12 uCi) (Protocol C).

From 1984 to 1987, 182 patients entered the study and 142 were considered evaluable. The 3-year disease free survival rate was 94.6% in protocol A patients, 85.6% in protocol B patients and 69% in protocol C ones. In protocol B, no significant difference in projected 3-year recurrence rate was found between DDP arm (13.3%) and control arm (14.7%). In protocol C, the projected 3-year recurrence rate was 21.8% in DDP arm and 37.6% in P32 arm; this difference was not significant. Acceptable toxicity was observed with both treatments. However, a longer follow-up is required to draw meaningful conclusions.

After a complete surgical staging, 30 patients with stage I ovarian carcinoma were treated by Piver *et al.* ([35]) with DDP at the dose of 1 mg/kg weekly for 4 weeks followed by combination chemotherapy with CTX (750 mg/mq i.v. day 1), ADM (50 mg/mq i.v. day 1) and DDP (50 mg/mq i.v. day 1) every 4 weeks for 5 courses. After a median follow-up of 34 months, 29 of them (97%) are alive with no evidence of disease and normal Ca-125 concentrations.

In our Department from 1982 to 1987, 18 patients with stage I ovarian carcinoma were observed. Patients with low malignant potential tumor or with simultaneous endometrial carcinoma were not considered. After accurate staging laparotomy, the 3 patients with stage IAi G1 carcinoma received no further therapy, while the other patients (with stage IAi G2-G3 tumor or with stage IAii-IBii-IC tumor) underwent postoperative chemotherapy. The drug therapy consisted of a monochemotherapy with CTX (800 mg/mq i.v. day 1) every 21 days for 12 courses in 3 patients; in a polychemotherapy with CTX (600-750 mg/mq i.v. day 1), ADM (45 mg/mq i.v. day 1) and DDP (50 mg/mq i.v. day 1) every 28 days for 6 courses in 4 patients; and in a polychemotherapy with CTX (600 mg/mq i.v. day 1) and DDP (50 mg/mq i.v. day 1) every 28 days for 6 courses in 8 patients. DDP containing regimens were routinely used after 1984. With a median follow-up of 54 months, recurrent disease was observed in 2 (11%) patients, one with stage IC tumor and the other with stage IBii tumor. The former showed progressive disease at second-look laparotomy performed at the end of chemotherapy with CTX alone; a second-line chemotherapy including ADM and DDP achieved no response, and the patient died 18 months after diagnosis. The other patient refused any further treatment after the second course of chemotherapy with CTX and DDP and relapsed 14 months after diagnosis. She continued to refuse any therapy and died 4 months later. In our series the 5-year actuarial survival rate was 89.2%. It is interesting to note that none of the 11 patients who were given 6 courses of DDP-based chemotherapy have developed recurrent disease, after a median follow-up of 54 months (range from 24 to 72 months).

CONCLUSIONS

Since a significant percentage of patients with completely resected early ovarian carcinoma relapse within 5 years from surgery, several types of postoperative treatments, including external radiotherapy, intraperitoneal isotopes instillation and systemic chemotherapy, have been employed in order to improve the survival rates ([13, 27, 35, 36]). These patients appear to benefit from adjuvant treatment, with the exception of those with stage IAi-IBi well differentiated disease, even if there is no agreement in literature about the superiority of a particular therapeutic approach ([26, 28, 37]). However the high response ra-

tes obtained in patients with advanced ovarian carcinoma with DDP containing combination chemotherapy have suggested the clinicians using such treatment also in early stage tumors.

Since there is an inverse relationship between the neoplasia size and its sensitivity to cytostatic drugs, DDP based regimens could represent the elective adjuvant therapy in surgically staged localized ovarian carcinoma ([38]).

REFERENCES

1) Helewa M. E., Krepart G. V., Lotocki R.. "Staging laparotomy in early epithelial ovarian carcinoma". *Am. J. Obst. Gyn., 154*, 282, 1986.
2) Bauchsbaum H. J., Lifschitz S.: "Staging and surgical evaluation of ovarian cancer". *Semin. Oncol., 3*, 227, 1984.
3) Piver M. S., Barlow J. J., Lele S. B.: "Incidence of subclinical metastasis in stage I and II ovarian carcinoma". *Obst. Gyn., 52*, 100, 1978.
4) Young R. C., Decker D. G., Wharton J. T., Piver M. S., Sindelar W. F., Edwards B. K., Smith J. T.: "Staging laparotomy in early ovarian cancer". *JAMA, 250*, 3072, 1983.
5) Fiorentino M. V., Nicoletto O., De Besi P., Stefani G., Tredese F., Vinante O., Fornasiero A., Cecchetto A., Maggino T., Marchesoni D., Nardelli G., Onnis A.: "Localized ovarian cancer: surgery plus chemotherapy". *Eur. J. Cancer Clin. Oncol., 22*, 1365, 1986.
6) Sall S., Stone M. L.: "The treatment of ovarian cancer". *Prog. Clin. Cancer, 5*, 249, 1973.
7) Fisher R., Young R.: "Advances in the staging and treatment of ovarian cancer". *Cancer, 39*, 967, 1977.
8) Piver M. S.: "Ovarian Carcinoma: a decade of progress". *Cancer, 54*, 2706, 1984.
9) Guthrie D.: "Early ovarian cancer: the European experience". In: "Multimodality treatment of ovarian cancer" (Conte P. F., Rosso R., Ragni N., Vermoken J. B. Eds.). Raven Press, pp. 87-93, New York, 1989.
10) Fuks Z.: "The role of radiation therapy in the management of ovarian carcinoma". *J. Med. Sci., 13*, 815, 1977.
11) Terada K. Y., Morley G. W., Roberts J. A.: "Pelvic irradiation for stage II ovarian carcinoma". *Gyn. Oncol., 29*, 26, 1988.
12) Dembo A. J.: "The role of radiotherapy in ovarian cancer". *Bull. Cancer (Paris), 69*, 275, 1982.
13) Hreshchyshyn M. M., Park R. C., Blessing J. A., Norris H. J., Levy D., Lagasse L. D., Creasman W. T.: "The role of adjuvant therapy in stage I ovarian cancer". *Am. J. Obst. Gyn., 138*, 139, 1980.
14) Dembo A. J., Bush R. S., De Boer G.: "Therapy in stage I ovarian cancer". *Am. J. Obst. Gyn., 141*, 231, 1981.
15) Dembo A. J., Bush R. S., Beale F. A., Bean H. A., Pringle J. F., Sturgeon J., Reid J. J.: "Ovarian carcinoma: improved survival following abdominopelvic irradiation in patients with completed pelvic operation". *Am. J. Obst. Gyn., 134*, 793, 1979.
16) Dembo A. J., Bush R. S., Beale H. A., Pringle J. F., Sturgeon J.: "The Princess Margaret study of ovarian cancer: stage I, II and asymptomatic III presentation". *Cancer Treat. Rep., 63*, 249, 1979.
17) Dembo A. J., Bush R. S., Beale F. A.: "A randomized clinical trial of moving strip versus open field whole abdominal irradiation in patients with invasive epithelial cancer of the ovary". *Int. J. Radiat. Oncol. Biol. Phys., 9 (suppl.)*, 97, 1983 (abstr.).
18) Dembo A. J.: "Radiotherapeutic management of ovarian cancer". *Semin. Oncol., 11*, 238, 1984.
19) Dembo A. J.: "Abdominopelvic radiotherapy in ovarian cancer a 10 year experience". *Cancer, 55*, 2285, 1985.
20) Dembo A. J.: "Radiotherapy in ovarian cancer". In: "Multimodality treatment of ovarian cancer" (Conte P. F., Rosso R., Ragni N., Vermoken J. B. Eds.), Raven Press, pp. 181-191, New York, 1989.
21) Leers W. H., Koch H. C. L. V.: "The evaluation of postoperative irradiation in patients with early stage ovarian cancer". *Gyn. Oncol., 28*, 41, 1987.
22) Piver M. S., Lele S. B., Pasner B., Krishnamsetty R., Emricnh L. J.: "Stage II invasive adenocarcinoma of the ovary: results of treatment by whole abdominal radiation plus pelvic boost versus pelvic radiation plus oral melphalan chemotherapy". *Gyn. Oncol., 23*, 168, 1986.
23) Piver M. S.: "Multimodality treatment in early ovarian cancer: the US experience". In: "Multimodality treatment of ovarian cancer" (Conte P. F., Rosso R., Ragni N., Vermoken J. B. Eds.), Raven Press, pp. 99-107, New York, 1989.
24) Smith J. P., Rutledge F. N., Delclos L.: "Postoperative treatment of early cancer of the ovary: a random trial between postoperative irradiation and chemotherapy". *Natl. Cancer Inst. Monogr., 42*, 149, 1975.
25) Dembo A. J., Bush R. S.: "Radiation therapy of ovarian carcinoma". In: Griffiths C.

T., Fuller A. F. (Eds.), "Gynecologic Oncology". The Hague, Martinus Nijhoff, pp. 263-298, 1983.
26) Davy M., Stenwig A. E., Kjorstad K. E., Berle E.: "Early stage ovarian cancer". *Acta Obst. Gyn. Scand., 64*, 531, 1985.
27) Klaassen D., Shelley W., Starreveld A., Kirk M.,Boyes D., Gerulath A., Levitt M., Fraser R., Carmichael J., Methot Y., Willian A.: "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., 6*, 1254, 1988.
28) Mackintosh J., Buckley C. H., Tindall V. R., Lind M. J., Anderson H., Crowther D.: "The role of postoperative alklating agent therapy in early-stage epithelial ovarian cancer". *Br. J. Obst. Gyn., 96*, 353, 1989.
29) Young R. C.: "A strategy for effective management for early ovarian cancer". In: Jones S. E., Salmon S. E., Eds., "Adjuvant therapy of cancer II". Grune and Stratton, pp. 467-474, New York, 1979.
30) Young R. C.: "Initial therapy for early ovarian carcinoma". *Cancer, 60*, 2042, 1987.
31) Cohen C. J., Goldberg J. D., Holland J. F., Bruckner H. W., Deppe G., Gusberg S. B., Wallach R. C., Kabakow B., Rodin J.: "Improved therapy with cis-platin regimens for patients with ovarian carcinoma (FIGO stages III and IV) and measured by surgical and staging (second-look operation)". *Am. J. Obst. Gyn., 145*, 955, 1983.
32) Vogl S. E., Pagan M., Kaplan B. H., Greenwald E., Arsenau J., Bennet B.: "Cis-platin based combination chemotherapy for advanced ovarian cancer small tumor burdens". *Cancer, 51*, 2024, 1983.
33) Milsted R., Sangster G., Kaye S., Calman K., Cordiner J., Soutter W., Barr W., Cunningham D., Sonkop M., Kennedy J.: "Treatment of advanced ovarian cancer with combination chemotherapy using cyclophosphamide, adriamycin and cis-platinum". *Br. J. Obst. Gyn., 91*, 927, 1984.
34) Bolis G., Marsoni S., Chiari S., Colombo N., Franchi M., Landoni F., Torri W., Zanaboni F.: "Cooperative randomized clinical trial for stage I ovarian carcinoma (OC)". In: "Multimodality treatment of ovarian cancer" (Conte P. F., Rosso R., Ragni N., Vermoken J. B. Eds.), Raven Press, pp. 81-86, New York, 1989.
35) Piver M. S., Malfetano J., Baker T. R., Lele S. B., Marchetti D. L.: "Adjuvant cisplatin-based chemotherapy for stage I ovarian adenocarcinoma: a preliminary report". *Gyn. Oncol., 35*, 69, 1989.
36) Bush R. S., Dembon A. J.: "Current status of treatment for patients with ovarian cancer". In: "Advances in the Biosciences. Ovarian Cancer". Oxford, Pergamon Press, 26, 115, 1980.
37) Pezner R. D., Stevens F. R., Tong D., Allen C.V.: "Limited epithelial carcinoma of the ovary treated with curative intent by the intraperitoneal installation of radiocolloids". *Cancer, 42*, 2563, 1978.
38) Young R. C., Knapp R. C., Fuks Z., Di Saia P. J.: "Cancer of the ovary". In: De Vita V. T., Hellman S., Rosemberg S. A., Eds., "Cancer: Principles and Practice of Oncology". ed 2., Philadelphia, Lippincott J. B., p. 1083, 1985.

Address reprint requests to:
Dr. A. GADDUCCI
Clinica Ostetrica e Ginecologica
Università degli Studi
Via Roma, 35 - 56100 Pisa