

● Brief Communication

FALLOPIAN TUBE CARCINOMA

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Twenty-one patients with fallopian tube carcinoma from Yale-New Haven Medical Center are reviewed. Most patients who died of disease did so in the first two years after diagnosis, even following complete resection, clearly indicating the need for adjuvant therapy. Negative second-look surgery did not provide assurance of permanent remission. There was a high recurrence rate with Stage I and completely resected Stage II and III disease (8 of 14 patients). Some recurrences occurred late, up to nine years after initial diagnosis. We recommend whole abdomino-pelvic radiation if no disease greater than 2 cm³ bulk exists after surgery. Chemotherapy may be an alternative to radiation as primary adjuvant treatment in early stage disease. Chemotherapy for unresectable disease or recurrent disease has shown palliation with occasional prolonged survival but no patient with recurrent disease survived longer than two years.

Fallopian tube carcinoma, Chemotherapy, radiation.

INTRODUCTION

Carcinoma of the fallopian tube is a rare cancer. Several staging systems, various surgical procedures, tumor grading systems and different methods of post operative management have been used. The experience with fallopian tube carcinoma at Yale New Haven Medical Center from 1952 to 1982 was reviewed. These patients accounted for 0.4% of all gynecologic malignancies at Yale.

Particular attention was directed to patient presentation, staging procedures, and the postoperative use of radiation and chemotherapy. A comparison of these findings with those in the literature is presented and recommendations are made for surgical staging and postoperative management.

METHODS AND MATERIALS

Records of all patients with the diagnosis of fallopian tube carcinoma in the hospital tumor registry and from the departments of Gynecology and Therapeutic Radiology were examined for the years 1952 to 1982. Twenty-one patients who had histologically confirmed fallopian tube adenocarcinoma were identified. In 11 patients the primary treatment was received at Yale New Haven Hospital. Seven patients were referred im-

mediately after diagnosis, and three patients were referred because of recurrence. All histologic slides were reviewed and satisfied the criteria for fallopian tube carcinoma outlined by Hu *et al.*²⁰ and modified by Finn and Javert¹⁴ (Table 1). The patients were all staged retrospectively according to a classification similar to the FIGO classification for ovarian carcinoma (Table 2) as advocated by Dodson *et al.*¹⁰

RESULTS

Patient characteristics

The average age of the patients at initial presentation was 55 years with a range from 34 to 82 years. Six patients were either nulligravid or primiparas (28.6%). The average parity was one with a range from 0 to 4.

The majority of patients presented with abnormal bleeding (52%), a pelvic mass (43%), or pain (38%), alone or in combination. One patient presented with abnormal cytology. Leukorrhea was found in three patients. One tumor was discovered incidentally during hysterectomy for stress urinary incontinence. Two tumors were found at laparotomy, one for presumed diverticulitis, and the other for presumed appendicitis. Another patient presented with an umbilical metastasis, and a right pelvic mass. The classic diagnostic triad for fallopian

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Table 1. Fallopian tube carcinoma criteria for diagnosis

1. The main tumor is in the tube and presents as a papillary growth
2. Microscopically—Chiefly the mucosa of the endosalpinx is involved
3. If the tubal wall is involved, the transition between benign and malignant epithelium should be demonstrated
4. The endometrium and ovaries must be normal, or have a benign lesion, or be involved in a malignant lesion which by histology, smaller size, or distribution is clearly metastatic from the tube

tube carcinoma of pain, bleeding, and leukorrhea was not found in any of our patients. However, a mass, bleeding and leukorrhea was present in two patients.

In eight of the 21 patients, the tumor mass was on the right side (38.1%) and in 12 on the left side (57.1%). One Stage IV patient had bilateral tumors at surgery.

Histology

Histologically, the tumors showed the alveolar, papillary, and medullary patterns that have been described for fallopian tube carcinoma. The size of the tumors varied from a few centimeters to large bulky masses that obliterated the terminal fimbria (Figure 1), with the distal and mid portion of the tube being most commonly involved. Histologically, 60% of the tumors were poorly differentiated (Figure 2) with scanty inflammatory reaction. In one case, extensive epithelial granulomata were present surrounding the tumor. Areas of *in situ* carcinoma and hyperplastic epithelial changes were seen in some well differentiated tumors (Figure 3). The remaining 20% of patients showed foci of both well and poorly differentiated carcinoma, and were therefore classified as moderately differentiated.

Table 2. Staging of fallopian tube carcinoma

Stage	Description
I	A Carcinoma confined to the fallopian tube
	B Disease confined to one fallopian tube; no ascites
	C Disease confined to both fallopian tubes; no ascites
II	A Disease confined to one or both fallopian tubes, ascites present with malignant cells in the fluid
	B Carcinoma extends to other intraperitoneal organs within the true pelvis
	C Disease extends to the uterus and/or ovary
III	A Disease extends to uterus and/or ovaries and to other intraperitoneal structures within the true pelvis
	B Disease in stage IIA or IIB: Ascites present with malignant cells in the fluid
	C Carcinoma extends to the uterus and/or ovaries and to other intraperitoneal organs beyond the true pelvis
IV	Carcinoma metastasizes to organs outside the peritoneal cavity

Second neoplasms

Three of the 21 patients subsequently developed second neoplasms; one squamous carcinoma of the chest wall, one papillary thyroid carcinoma and one carcinoma of the breast. One carcinoma of the ovary of borderline malignant potential was found in association with a poorly differentiated fallopian tube carcinoma. This last case was found at the time of surgery for the fallopian tube cancer whereas the other three developed later.

Methods and management

The primary therapy for fallopian tube carcinoma was surgical. Patients were categorized into three therapy regimens—surgery alone, surgery with postoperative radiation, and surgery with postoperative chemotherapy. The median follow-up time from diagnosis was four years, with a range of 7 months to 23 years.

Surgery. When primary surgery was performed at Yale New Haven Medical Center, a staging laparotomy and debulking procedure was done as in ovarian cancer management. Seventeen patients had primary total abdominal hysterectomy and bilateral salpingo-oophorectomy. Eight of these patients also had a subcolic omentectomy and one patient had an omental biopsy. Of the four remaining patients, one had a bilateral salpingo-oophorectomy, and in one, tumor was found at vaginal hysterectomy for stress urinary incontinence, and she then underwent exploratory laparotomy, bilateral salpingo-oophorectomy and omental biopsy. In two patients, laparotomy was performed for the evaluation of pelvic pain and the fallopian tube was found to be involved with carcinoma. Hysterectomy and removal of the remaining adnexa was performed as a secondary procedure in each of these patients.

Two patients with Stage II disease and one patient with Stage III disease had surgery as their only therapy. Recurrence developed in one Stage II patient at 7 years and within a year in the Stage III patient.

Radiation. Postoperative radiation was employed in 14 patients; five with Stage I, six with Stage II, and three with Stage III disease. Patients were treated with a 2 MeV Van de Graff generator, a 6 MeV or 25 MeV linear accelerator. Either pelvic or whole abdominopelvic fields were treated using open field techniques. One patient received pelvic and paraaortic irradiation. If treated, the upper abdomen usually received 2000 rad via anterior-posterior and opposed fields at doses of 140–150 rad per day. Pelvic fields were treated with antero-posterior opposed fields at 180 rad per day to total doses of 4000 to 4500 rad. A boost of 400 rad in 2 treatments were given to the site of residual bulk pelvic disease in one patient. Intrauterine radium was employed in two patients after bilateral salpingectomy and one of these patients also received external beam pelvic irradiation. One patient was given post-operative

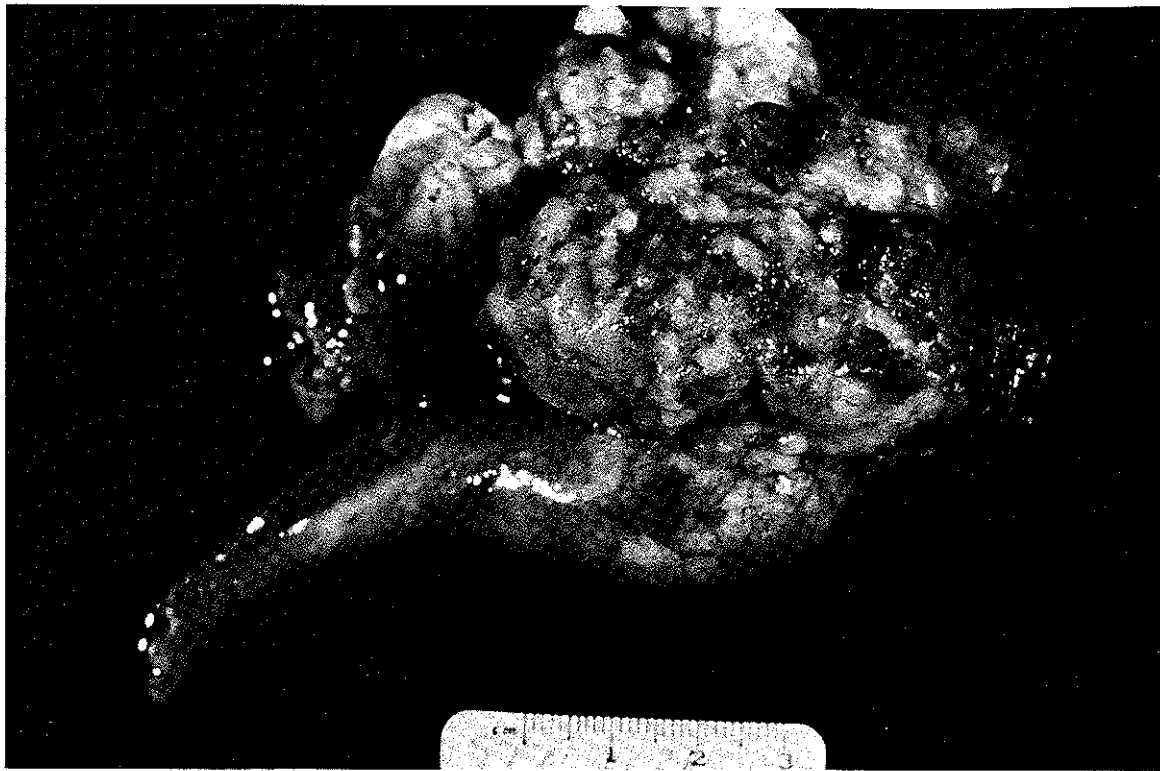


Fig. 1. Gross picture of a fallopian tube carcinoma showing a cauliflower-like tumor mass involving the mid and distal portion of the tube.

external beam therapy and radium application for a fallopian tube cancer incidentally found at the time of vaginal hysterectomy.

Chemotherapy. Chemotherapy was used as postoperative adjuvant treatment in four patients. The regimens used were individualized by the treating gynecologist

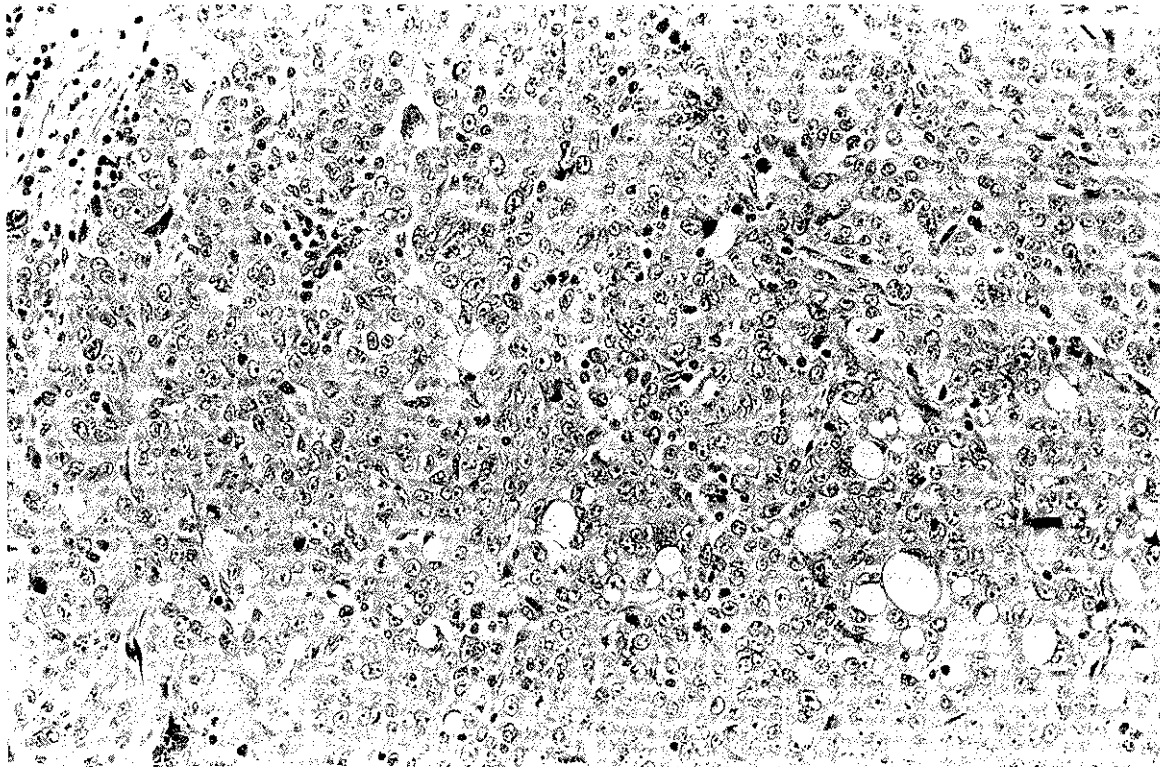


Fig. 2. Poorly differentiated carcinoma mitotic figures are prominent (H&E 250X).

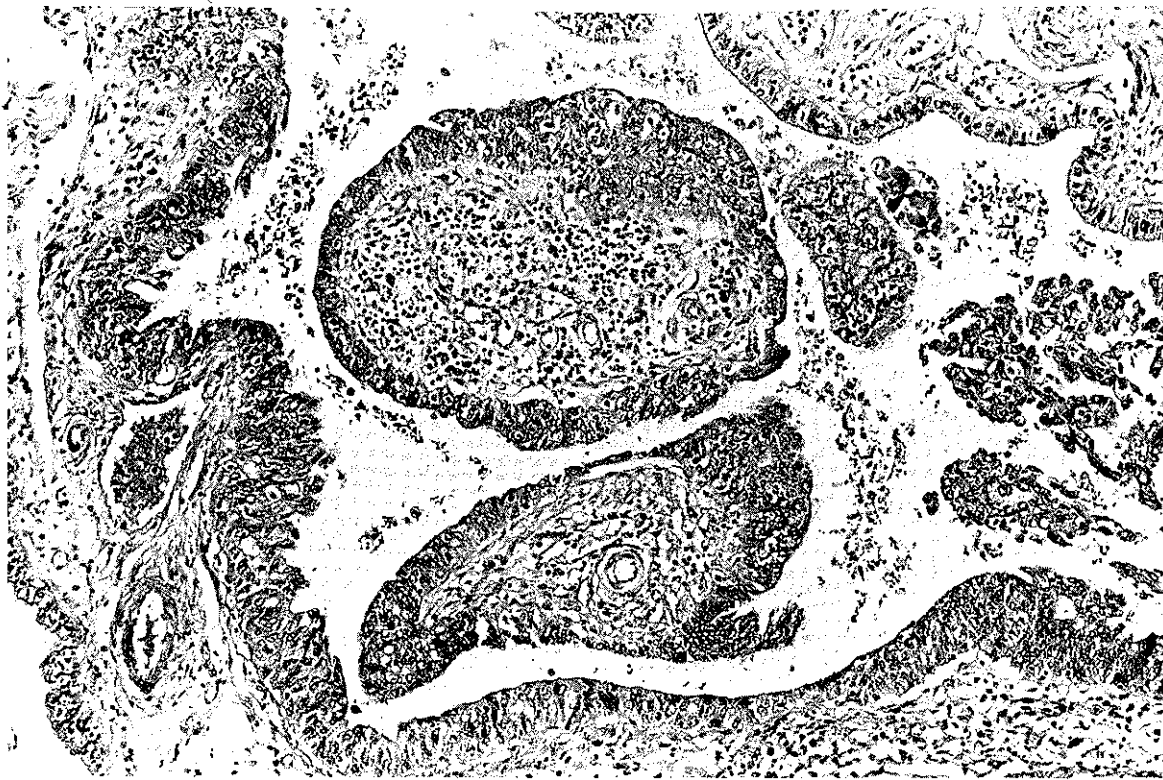


Fig. 3. Areas of *in situ* carcinoma were present in some of the well differentiated cancers (H&E, 200X).

and reflected the drugs used for ovarian cancer at the time of management. Primary therapy in the early and mid 1970's included cyclophosphamide and melphalan; towards the late 1970's doxorubicin and cis-platinum became more widely used.²⁴ In addition, progestational agents have been added.³⁴

Melphalan was used as a single agent in one patient with Stage I disease. Combination cytotoxic drugs and progestins were used for all other stages. The dosage of the cytotoxic agents was calculated according to body surface area and adjusted according to individual toxicity. Treatment was given every month if possible, for 18 courses. Complete blood profiles were obtained prior to each treatment. Left ventricular ejection fractions were obtained prior to initiation of doxorubicin therapy. This was repeated after six courses of therapy and before each treatment after a cumulative dose of 450 mg/m² had been reached.

Recurrence. As in previous reports of fallopian tube carcinoma, a high recurrence rate was also found in this series.³⁰ Two Stage I, four Stage II, and three Stage III patients developed recurrence when no gross residual disease was noted after primary treatment (38%). Radiotherapy was given for recurrence in three patients, chemotherapy in three patients, and a combination of the two in two patients. No patient with recurrence survived longer than two years from the time of recurrence. Radiation therapy was directed to the areas of known disease including the spleen, groin, femur, brain,

and pelvis (if these areas had not been previously irradiated). Melphalan was used in one case, and combination chemotherapy was used in the others.

Results of treatment

Stage I. Five of the Stage I patients received adjuvant postoperative radiation and one received melphalan. Three Stage I patients who received radiation had long term survival. In two of these patients, the uterus had been left for radium placement and the other received pelvic and paraaortic radiation along with intravaginal radium. One patient has no evidence of disease 7 months following completion of abdomino-pelvic radiation. A patient with complete resection of tumor, but with tumor spill at the time of surgery who was treated with postoperative pelvic radiation, developed recurrence at six months and died. The one patient who received 12 courses of melphalan developed recurrence at 18 months following chemotherapy and has been treated with abdomino-pelvic irradiation.

Stage II. Nine patients had Stage II disease. Three who underwent surgery and postoperative radiation are disease-free from three to 23 years later. Two of these 3 received abdomino-pelvic irradiation and one received pelvic radiation alone.

One patient was treated with combination chemotherapy and had a negative second-look operation. She has remained disease-free four months thereafter. An-

other patient who had surgery alone is without disease 21 years later.

Four of the nine patients with Stage II disease died; three from recurrent tumor and one from surgical complications. Three of the recurrences were late at six, seven, and nine years after diagnosis. At the time of recurrence, multiagent chemotherapy was given to all three patients. An objective response was documented in two patients. The first had a splenic recurrence treated with surgery and radiation, but tumor persisted. After reoperation she was given combination chemotherapy but died following complications from her prior surgery. No tumor was found at postmortem. The other patient who had responded to chemotherapy had lung metastases which completely resolved within three months of her treatment. She remained in remission for 18 months but eventually died of disease two years later.

Stage III and IV. Five patients had Stage III disease and one patient had Stage IV disease. Postoperatively, three received abdomino-pelvic radiation, two received combination cytotoxic and progestin therapy, and one patient had no treatment. The longest survivor had residual disease following surgery and remains alive and free of clinical disease 11 years after abdomino-pelvic radiation. The other two patients given abdomino-pelvic radiation died within one year, although they had no clinical evidence of disease following surgery. Both patients who received postoperative combination chemotherapy died. One had a large amount of residual disease, and the other had no residual tumor after surgery. The latter patient had a negative second-look procedure one year after completion of her chemotherapy but developed recurrence in her groin three years later. This responded to external beam radiation. The patient later died from squamous cell carcinoma arising from the chest wall. Her original pathology lacked a squamous component. The patient who was not given treatment postoperatively, and who had a large amount of residual disease, required palliative radiation to control recurrent vaginal bleeding.

DISCUSSION

The diagnosis of fallopian tube carcinoma should be considered in women with abnormal vaginal bleeding, especially postmenopausal bleeding, when endometrial sampling and cervix biopsy is not diagnostic,^{13,21} even if there is no pelvic mass. Fallopian tube carcinoma becomes symptomatic earlier and presents with disease confined to the pelvis more frequently than ovarian carcinoma.²² Occasionally patients with fallopian tube carcinoma present only with positive cytology.^{6,31} Late stages are associated with poor prognosis. Therefore early diagnosis and accurate surgical staging are of paramount importance in objectively assessing prognosis and in planning therapy. Prior to 1970, thorough ab-

dominal exploration, including biopsy of suspicious pelvic or paraaortic nodes, biopsy of adhesions, omental biopsies, and abdomino-pelvic cytology now customary for ovarian staging was not routinely performed. This suggests that recurrence in Stage I or II disease, may have been a result of growth of the original understaged tumor. The frequency of nodal involvement in fallopian tube carcinoma is unascertained. Tamini and Figge³⁶ cited two cases with apparent early stage disease where periaortic nodes were the only sites of metastasis. Their total frequency of node involvement was 53%. They advocated nodal sampling, especially of the periaortic nodes at the time of surgery, and recommended treatment of areas beyond the pelvis.

Different staging systems for fallopian tube carcinoma have been proposed.^{12,32} Several of these noted the anatomic similarity of the fallopian tube to bowel. Since fallopian tube carcinoma is similar to ovarian carcinoma in presentation, mode of dissemination, and response to therapy, a classification similar to the FIGO classification for ovarian carcinoma¹⁰ is used in this paper. One difficulty with the use of this staging system was with spread of early carcinoma of the fallopian tube to the mesosalpinx, i.e., broad ligament. Such spread was regarded here as spread outside the tube, but such a concept may be controversial and the issue needs resolution.

Seventeen patients were available for five year survival analysis yielding a five year survival rate without recurrence of 47%. For Stage I the five year survival was 60%, Stage II 66%, and Stage III and IV combined 16%. Other series in the literature shows survival rates ranging from 20 to 44%.^{3,5,11,17,18,20,26-30,32,33,36,37} Such 5 year survival data have little significance in a disease that has frequent late recurrence.

Most patients who died of disease did so in the first two years after diagnosis, even if the neoplasm was apparently confined to the tube at initial surgery, and a complete resection had been performed.³³ However, disease may recur late; in the present series there were three patients with recurrence at six, seven and nine years after initial diagnosis. The five year survival may therefore not fully reflect the effectiveness of therapy. A negative second-look operation may not provide assurance of permanent remission, as has also been found in ovarian carcinoma. In the present series of fallopian tube carcinomas, there were four negative second-look operations and two of these patients developed recurrent disease, three and six years after diagnosis.

Radiation therapy

The role of postoperative radiation therapy is difficult to delineate clearly from a review of the literature. The lack of uniform staging techniques and the selectivity of patient referrals for irradiation therapy which often employed suboptimal equipment and radiation dosage

to inappropriate treatment volumes, compounds the problems in interpreting the earlier literature.

A review of the experience of the management of fallopian tube cancer in 3 Danish Radium Centers revealed a 2.5 year survival rate of 60% with high voltage X rays versus a 30% survival rate following conventional X rays.¹⁵ Boutselis and Thompson⁵ reported beneficial effects of postoperative irradiation in 7 out of 8 patients, with four of the 8 patients so treated alive and free of disease at periods of 2 to 9 years. The routine use of post-operative external beam radiation therapy was advocated by Phelps and Chapman²⁸ for patients with disease clinically limited to the pelvis, and a 89% survival rate was reported in patients with Stage I and II disease (followed for 1.5 to 16 years). Employing postoperative megavoltage irradiation to the pelvis, Benedet *et al.*³ noted that 7 of 10 patients were alive and well, while 4 of 6 patients treated with curative intent to the pelvis and paraaortic nodes also survived. Similarly, Henderson *et al.*¹⁹ noted a 50%, 5 year survival rate (3/6) in patients treated with postoperative pelvic irradiation therapy. The results presented in the current study support the value of postoperative external beam radiation therapy. Nine patients, 5 with Stage IIB or III disease, were treated with abdomino-pelvic⁸ or pelvic and aortic¹ irradiation and 5 of these remain free of disease. Of the 5 patients who received more limited uterine or pelvic irradiation for Stage I or IIA disease, 3 have failed, two only in the upper abdomen. Amendola *et al.*¹ also noted failures in 6 of 11 patients treated with postoperative pelvic irradiation for Stage I disease. A high incidence of peritoneal and omental involvement was noted in that series. Roberts and Lipshitz³⁰ also failed to show any benefit of postoperative pelvic irradiation in Stages I and II disease.

The optimal radiation time-dose-volume parameters remain to be delineated. Review of the patterns of spread in fallopian tube cancers^{3,19} suggests that it is similar to ovarian cancer. Therefore, the entire peritoneal cavity, including the diaphragms and paraaortic nodes is the volume at risk for microscopic dissemination and recurrence, particularly in the advanced stages. Radiation therapy to whole abdominal fields employing doses similar to those advocated for ovarian cancer should be considered in all patients with minimal postoperative residual disease.

A retrospective analysis of the results of treatment of 2115 patients with ovarian cancer at the M. D. Anderson Hospital³⁵ compared their results of treatment with postoperative radiation therapy to results of treatment with chemotherapy (mainly single agent). When stage of disease, size of postsurgical residual disease, and histological grade were taken into account, an improved survival was noted for patients treated with radiation therapy as opposed to single agent chemotherapy. Furthermore, a randomized prospective trial in ovarian

cancer from the Princess Margaret Hospital⁸ showed improved survival in patients with Stage I, Stage II and asymptomatic Stage III disease treated with abdomino-pelvic irradiation compared to those treated by either pelvic irradiation alone or pelvic irradiation plus chlorambucil.

Several reports describe the use of radioactive colloidal phosphate (³²P) in the treatment of fallopian tube carcinoma. Benedet *et al.*³ used ³²P where no macroscopic disease was present in the peritoneal cavity in two patients (Stage IIA and B). They were alive at 5 months and 24 months with no complications from instillation and no evidence of recurrence. The use of ³²P in fallopian tube carcinoma warrants further investigation.

Chemotherapy

Chemotherapy has played a role primarily in the treatment of patients with recurrent disease or in patients with bulk residual disease that could not be removed at surgery. Yoonesi³⁷ reviewed the earlier literature. The drugs used generally reflect the chemotherapy use prevalent at the time for ovarian carcinoma. Five fluorouracil,^{10,19} melphalan^{3,4,10} chlorambucil^{16,25,29} cytoxan,^{3,7,25,29} actinomycin D with cytoxan and 5-fluorouracil,¹⁹ adriamycin,¹⁶ hexamethylmelamine,²⁹ methotrexate²⁹ and cisplatin^{9,29} have all been advocated. With Stage I disease, chemotherapy was always given in conjunction with radiation therapy.^{10,25,29} The patient, reported in this series, given melphalan is the only documented case of the use of single agent chemotherapy as primary treatment in Stage I, as an alternative to radiation therapy. This patient had recurrence within 18 months. Boronow⁴ and Raju and Wiltshaw²⁹ used chemotherapy for recurrent disseminated Stage I disease and obtained good response.

Raju and Wiltshaw²⁹ used chemotherapy for recurrence after radiation failure in patients with Stage II disease and reported a survival range of 2 years 6 months to 8 years. Guthrie and Cohen¹⁶ described one patient who underwent right salpingo-oophorectomy with documented residual disease who was treated with adriamycin, cytoxan and progesterone. Second look surgery was negative and the patient had no evidence of disease after 3 years. Long term survival for Stage III disease has not been documented with either single or multiagent chemotherapy. Deppe *et al.*⁹ described two patients with post-operative residual disease who had no clinical sign of recurrence 6 months and 9 months, respectively, after negative second look surgery following chemotherapy with doxorubicin, cisplatin and progesterone. It would be of interest to know if this survival was further prolonged because of the incidence of late recurrence. Raju and Wiltshaw²⁹ reported palliation in two patients given post-operative cisplatin and alkeran. The longest survivor with Stage III disease was a patient who underwent a bilateral salpingo-oophorectomy, was given cy-

toxic and survived for 69 months.³ There are several reports of patients living for 8 to 12 months with Stage III disease⁴ following chemotherapy.^{7,19} Some patients with Stage IV disease treated with radiation and chemotherapy survived for as long as 2 years.^{3,10} Kadziora and Srinivasan²³ described a patient with pulmonary metastases who, after left salpingectomy, received intrathoracic thiotepa and systemic melphalan and progesterone and at the time of report had survived at 2½ years. In the Yale series, chemotherapy was used for recurrence in 3 Stage II cases and one Stage IV patient. Survival was prolonged from 2 to 5 years for Stage II patients and only a few months in the patients with Stage III and IV disease. It therefore appears that chemotherapy is useful as palliation for recurrent or advanced disease. Its use as primary therapy, as an alternative to radiation, has not been tested. Its role in the management of early completely resected fallopian tube carcinoma^{2,3,4,7,9,10,16,19,23,25,29,37} needs to be investigated, but it would appear that combination chemotherapy rather than single agent therapy will need to be used.

Progestational agents

The use of progestational agents in fallopian tube carcinoma was first advocated by Smith³⁴ and has found widespread use. The rationale for its use appears tenuous, although cyclic changes similar to those in endometrium have been documented in tubal epithelium.⁷ Steroid receptors were identified in one of two patients in the present series. Since chemotherapy has been found to

be useful in the management of recurrence, progestational agents have been added to the cytotoxic drugs used, particularly as there is no additional toxicity.

CONCLUSION

The initial therapeutic approach for patients with fallopian tube carcinomas should be surgical and should include removal of readily excisable tumor. A complete assessment of the extent and volume of residual disease is essential just as in ovarian cancer management. The value of aggressive debulking procedure has not been proven.

The high rate of relapse following surgery in fallopian tube carcinoma alone suggests the use of abdominopelvic radiation therapy as adjuvant postoperative treatment in patients with minimal residual disease. Additional radiation therapy to the pelvis, the para-aortic nodes, and other sites of potential microscopic residual disease should be considered.

The role of adjuvant chemotherapy is less well defined, but appears analogous to its use in ovarian cancer. Chemotherapy is beneficial in patients with gross residual disease and with recurrent cancer. Good responses have been observed, but five year survival data are not available at this time. The use of chemotherapy for unresectable disease or for recurrent early stage disease has shown palliation with occasional prolonged survival.

There is a need for controlled, multi-institutional studies to clarify the roles of debulking surgery, postoperative radiation and chemotherapy in the management of fallopian tube carcinoma.

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