

GYNECOLOGIC ONCOLOGY GROUP • HEADQUARTERS

OPERATIONS OFFICE 1234 MARKET STREET • SUITE 1945 • PHILADELPHIA, PA 19107 • 215-854-0770
STATISTICAL OFFICE R.P.M.I. APTS • R.P.M.I. • 666 ELM STREET • BUFFALO, NY 14263 • 716-845-5702

PROTOCOL GOG #94

A PHASE II STUDY OF THE TREATMENT OF PAPILLARY SEROUS CARCINOMA
OF THE ENDOMETRIUM STAGE I AND II AND MAXIMALLY DEBULKED
ADVANCED ENDOMETRIAL CARCINOMA WITH TOTAL ABDOMINAL

RADIATION THERAPY

(CATEGORY II - 3 POINTS)

NAV1.954711.002

STUDY CHAIRMAN

JANICE H. AXELROD, M.D.
DIVISION OF GYNECOLOGIC ONCOLOGY
SAINT LOUIS UNIVERSITY
1325 SOUTH GRAND BLVD.
ST. LOUIS, MISSOURI 63104
(314) 577-8755

STUDY CO-CHAIRMEN

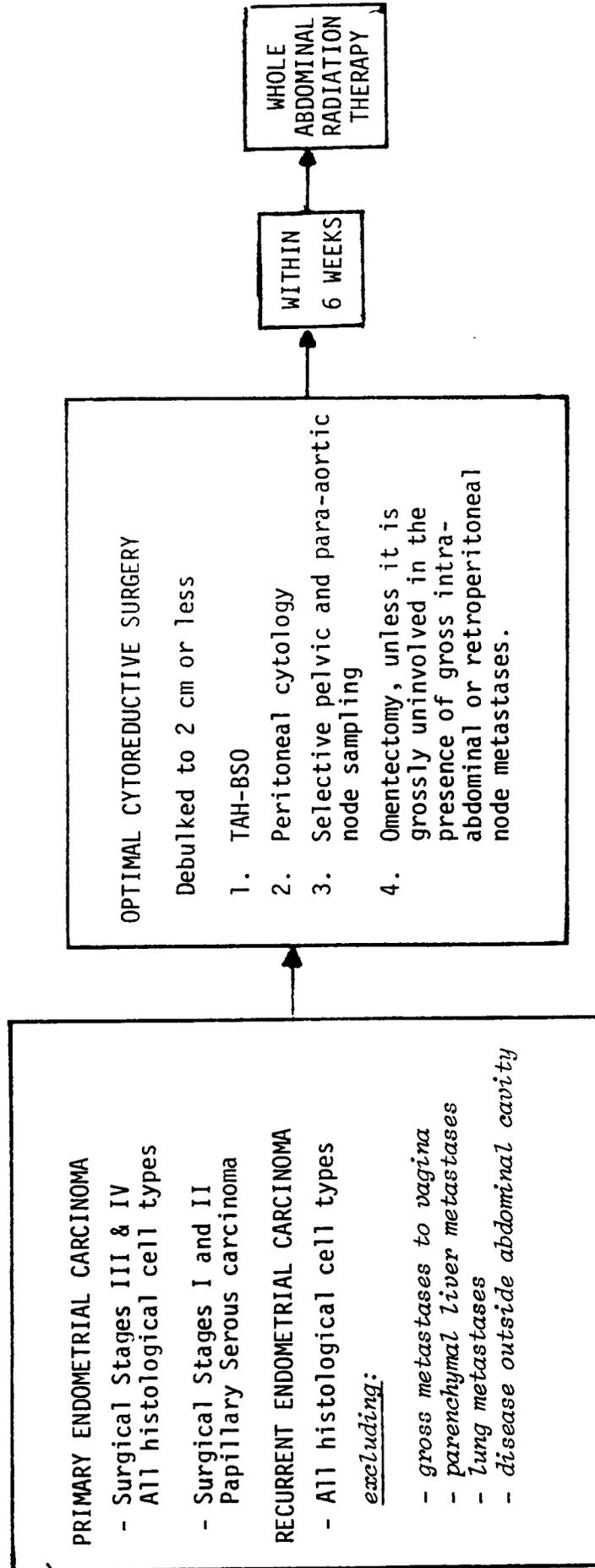
TAPAN ROY, M.D.
DEPARTMENT OF RADIATION ONCOLOGY
SAINT LOUIS UNIVERSITY
1325 SOUTH GRAND BOULEVARD
ST. LOUIS, MO 63104
(314) 577-8000 Ext. 3291

MARY KING, M.D.
DEPARTMENT OF PATHOLOGY
UNIVERSITY OF ILLINOIS
HOSPITAL
840 SOUTH WOOD STREET
CHICAGO, IL 60612
(312) 996-3877

ACTIVATED DECEMBER 22, 1986

A PHASE II STUDY OF THE TREATMENT OF PAPILLARY SEROUS CARCINOMA OF THE
 ENDOMETRIUM STAGE I AND II AND MAXIMALLY DEBULKED ADVANCED
 ENDOMETRIUM CARCINOMA WITH TOTAL ABDOMINAL RADIATION THERAPY

S C H E M A



1.0 OBJECTIVES

- 1.1 To determine the survival and progression free interval of patients with maximally debulked advanced endometrial carcinoma treated with abdominal radiation therapy.
- 1.2 To determine the progression free interval and site of recurrence in patients with Stage I and II papillary serous carcinoma of the endometrium treated with abdominal radiation therapy with pelvic boost.

2.0 BACKGROUND AND RATIONALE

In regard to Objective 1.1:

Advanced endometrial carcinoma, Stage III and Stage IV accounts for 10% of all patients with endometrial carcinoma. There are additional patients, clinically Stage I or Stage II, who on surgical evaluation have more advanced disease, disease not readily cured by total abdominal hysterectomy and bilateral salpingoophorectomy and pelvic radiotherapy. According to 1985 data obtained from GOG Protocol #33,¹ 6.3% of patients with Stage I or II had adnexal spread of disease. The peritoneal cavity was involved by gross tumor in 6.1% of patients - 1.5% by gross serosal breakthrough of the uterus, 1.8% by pelvic implants and 2.8% by extrapelvic implants. Danoff et al² evaluated 32 patients with Stage III disease. She divided them into 2 groups: 19 patients with "clinical Stage III" and 13 patients with "pathologic Stage III". The crude five year survival was 11.7% and 44% respectively. The most common evidence of distant metastasis in patients with clinical Stage III was diffuse intraperitoneal metastasis with tumor involving the omentum, mesentery, small bowel and peritoneum. Yoonessi et al³ reported on 20 of 64 patients who died with distant or distant and local metastasis. The distant metastasis were carcinomatosis with or without ascites and involvement by the omentum. In his review of adenocarcinoma of the endometrium, Howard Jones⁴ recommended primary

exploration and total abdominal hysterectomy and bilateral salpingoophorectomy in clinical Stage III patients. Occasionally the adnexal mass is benign or primary ovarian carcinoma. He stressed that a correct diagnosis and documentation of the full extent of disease is essential to develop a treatment regimen. However, his experience with whole abdominal radiation therapy was small and disappointing. He therefore advocated treatment of Stage IV disease with progestational agents.

Progestational agents have, however, been somewhat disappointing. Jones⁴ cites an overall objective response rate of 20-40%. Most of these responses are in patients with well differentiated tumor. There was an overall response rate of only 14% in a GOG study⁵ of patients with advanced or recurrent endometrial carcinoma treated with medroxyprogesterone acetate. The response also correlated with grade, the well differentiated tumors responding better than the poorly differentiated tumors. Since 73% of Stage III tumors are Grade II (54%) and Grade III (19%), the expected response to progestins is quite poor.⁶

Systemic chemotherapy has been equally disappointing. GOG Phase II trial⁷ of cis-Platinum had only a 4% objective response (one partial response) among patients with measurable advanced or recurrent endometrial cancer. A response rate of 36.8% was noted in combination chemotherapy for two regimens - melphalan and 5-fluorouracil or doxorubicin, 5-fluorouracil and cyclophosphamide.⁸ Preliminary response data on patients treated with either doxorubicin or doxorubicin and cyclophosphamide (GOG 48)¹ reveals only a 25.3% response rate (10.4% CR, 14.9% PR). Conclusions drawn are that "the combination of doxorubicin plus cyclophosphamide appears to offer no advantage over doxorubicin alone in the management of endometrial carcinoma."

In a highly selected patient group radiation therapy appears promising. Greer and Hamberger⁹ reported a corrected 5 year survival of 80% and absolute 5 year survival of 63% among 27 patients with intraperitoneal metastatic adenocarcinoma of the endometrium, who had 2 cm or less residual

disease at laparotomy, and postoperative treatment of whole abdomen by moving strip technique with pelvic boost irradiation. Twelve patients with incidental metastatic disease did better than those 15 patients maximally debulked to 2 cm or less (5 year survival 91%, 71% respectively). The distribution of tumor grade was Grade 1 - 5 patients; Grade 2 - 16 patients; and Grade 3 - 4 patients. There was no difference in survival by grade of the tumor. Major complications included two patients developing severe enteritis requiring cessation of therapy. Major late complications included one patient with a vaginal ulcer, one patient with a partial small bowel obstruction and rectal bleeding managed conservatively, and one patient with small bowel obstruction requiring surgical correction, with a later development of an enterocutaneous fistula also surgically corrected.

Of six patients with recurrence, three developed recurrence inside of the treatment field, two developed recurrence outside the treatment field, and one developed recurrence in both areas. No data are currently available for systemic therapy in such a highly selected patient population.

In summary advanced endometrial carcinoma, "surgical stage" III and IV limited to the abdomen, in small series, appear to have a favorable response to total abdominal radiotherapy if maximally debulked at laparotomy to 2 cm or less.

A Phase II trial of total abdominal radiation therapy in treating patients with endometrial carcinoma with abdominal metastasis, maximally debulked to 2 cm or less, is therefore proposed to attempt to confirm the excellent results by Greer and Hamberger.

In regard to Objective 1.2:

Papillary serous adenocarcinoma of the endometrium has also been recently identified as a clinically aggressive variety of endometrial carcinoma. Hendrickson et al¹⁰ reviewed 256 Stage I endometrial carcinomas and identified 26 as uterine papillary serous adenocarcinoma. Fifty percent of

these 26 patients relapsed (five times the rate of classical endometrioid carcinoma of the endometrium). Six of 7 failures in the upper abdomen were uterine papillary serous carcinoma (6/26 papillary serous tumors failed in the upper abdomen). There were an additional 26 patients with more advanced papillary adenocarcinomas which were followed. Of these, 11 presented or relapsed with abdominal carcinomatosis. Only four of these 26 patients survived. The authors recommended adjuvant upper abdominal radiation therapy or chemotherapy. Sato et al¹¹ reviewed 229 patients with endometrial carcinoma. Eight of these patients had papillary serous adenocarcinoma. Only 3/8 had Stage I disease; 3/8 had Stage III and 2/8 had Stage IV. This contrasts sharply with 80% rate of Stage I ordinarily seen with endometrial carcinoma. This papillary tumor was also associated with deep myometrial involvement in 50% of the cases. Walker and Mills¹² demonstrated 6/11 patients with papillary serous carcinoma had either Stage III or IV disease. Lauchlan¹⁴ proposed that early lymphatic and vascular involvement was responsible for frequent dissemination of disease even in the absence of deep myometrial involvement. Hendrickson¹⁰ cited the tendency of tumor to spread over the peritoneal surfaces in a manner similar to ovarian carcinoma.

Because of the aggressiveness of papillary serous carcinoma of the endometrium, with frequent relapses and spread in the upper abdomen and poor response of endometrial carcinoma in general to progestational agents and systemic chemotherapy, it is proposed that Stage I and II papillary serous carcinoma variants be included. However, this subset of patients will be evaluated separately in order to detect differences in progression free interval and site of recurrence.