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PROTOCOL GOG #99

A PHASE III RANDOMIZED STUDY OF ADJUNCTIVE
RADIATION THERAPY IN INTERMEDIATE RISK ENDOMETRIAL ADENOCARCINOMA

(CATEGORY I -- 6 CREDITS)

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ENCLOSURE (17)

SCHEMA

A PHASE-III RANDOMIZED STUDY OF ADJUNCTIVE
RADIATION THERAPY IN INTERMEDIATE RISK ENDOMETRIAL ADENOCARCINOMA

ENDOMETRIAL
ADENOCARCINOMA
ALL CELL TYPES*
SURGICAL STAGE I

- TAH-BSO
- SELECTIVE PELVIC NODE SAMPLING
- SELECTIVE PARA-AORTIC NODE SAMPLING
- PERITONEAL CYTOLOGY

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REGIMEN I
NO ADDITIONAL
TREATMENT

REGIMEN II
5040 cGY TOTAL
PELVIC RT (TPR)
MUST BEGIN NO LATER
THAN 8 WEEKS AFTER
SURGERY

* EXCEPT PAPILLARY SEROUS AND CLEAR CELL CARCINOMA AND GRADE 1 ENDOMETRIAL ADENOCARCINOMA

1.0 OBJECTIVES

- 1.1 To determine if patients with intermediate risk endometrial adenocarcinoma (as defined below), who have no spread of disease to their lymph nodes, benefit from postoperative pelvic radiotherapy.
- 1.2 To evaluate how the addition of pelvic radiotherapy will alter the site and rate of cancer recurrence in these intermediate risk patients.

2.0 BACKGROUND AND RATIONALE

The treatment of endometrial adenocarcinoma has evolved from a regimen of complete pelvic radiotherapy followed in six weeks by an extrafascial hysterectomy to an often customized program which is determined by the presence or absence of several risk factors. The importance of various risk factors was pointed out as a result of the findings of GOG P-1(1-3). As a result of this work, depth of myometrial invasion, nodal involvement, cervical involvement, positive peritoneal cytology, grade of the tumor, tumor location, etc., were considered to be potential risk factors. Thus, patients whose malignancy manifested these factors were often given postoperative radiotherapy. In many cases these risk factors were viewed as being of equal importance in predicting the presence of advanced disease for which additional therapy would be needed.

In an effort to expand this pilot study, a registry protocol (GOG #33) was started. 931 evaluable patients were obtained in this study(4). An extensive mathematical analysis of the data from this protocol has demonstrated numerous risk factors of differing mathematical importance.

The factor which shows the highest risk is paraaortic node involvement. While this mathematical model suggested that pelvic nodal involvement is a non-risk factor, clinical knowledge suggests otherwise. Thus, the absence of these two factors was necessary to define an intermediate risk group. When the data are reevaluated with these two factors absent, it is found that adnexal spread and/or positive cytologic washings was the only remaining high risk factor which had clinical support(5,6). Thus, this was removed from the definition of intermediate risk cancer.

On the other end, suspicious washings, no myometrial invasion and Grade 1 differentiation were non-risk factors and do not fit into the definition of intermediate risk endometrial cancer. When the remaining "intermediate" risk factors are evaluated for clinical importance, it is found that the true intermediate risk group is women who have myometrial invasion with no associated high-risk factors. Thus, it is this group who will make up the basis of this study. The estimate of expected recurrence for intermediate risk is 80% disease-free survival at 5 years.

If a study of this nature can demonstrate that these intermediate risk patients do not benefit from pelvic radiotherapy, the additional morbidity and expense can be eliminated from the treatment regimen of these patients. This will decrease the use of extra lab work ordered and again decrease health care costs. In addition, the recurrence site data will allow the identification of those follow-up studies which will be most helpful in these patients.

3.0 PATIENT ELIGIBILITY AND EXCLUSION

3.1 Eligible Patients

- 3.11 Patients with primary histologically confirmed Grades 2 and 3 endometrial adenocarcinoma (endometrioid, villoglandular, mucinous and adenosquamous).
- 3.12 Patients must have had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic node sampling, pelvic washings and are found to be surgical Stage I.
- 3.13 Patients must have myometrial invasion.
- 3.14 Patients with adequate bone marrow, renal and hepatic function: WBC 3,000 or greater, platelets 100,000 or greater; creatinine 2.0 mg% or less; bilirubin and SGOT equal to or less than 2 x normal.
- 3.15 Patients with a GOG Performance Status of 0, 1 or 2.
- 3.16 Radiation therapy must begin no later than 8 weeks after surgery in those patients randomized to radiation.
- 3.17 Patients who have signed a consent form.
- 3.18 Patients who have met the pre-entry requirements specified in Section 7.0.

3.2 Ineligible Patients

- 3.21 Patients with previous or other concomitant malignancy except of skin (excluding melanoma).
- 3.22 Patients who have had prior or preoperative pelvic radiation.
- 3.23 Patients who have had prior or preoperative chemotherapy.
- 3.24 Patients with pathologically confirmed spread of disease to (1) pelvic or para-aortic lymph nodes; (2) beyond the pelvis; (3) to the adnexal structures; (4) to the cervix.
- 3.25 Patients with positive cytologic washings.
- 3.26 Patients who in the opinion of the surgeon are felt to be at a significant increased risk if they receive adjuvant radiation therapy.
- 3.27 Patients with papillary serous and clear cell carcinoma.
- 3.28 Patients with Grade 1 endometrial adenocarcinoma.

4.0 STUDY MODALITIES

4.1 Surgical Procedure

All patients will undergo a total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy. Peritoneal cytology will be obtained on entering the peritoneal cavity. (Appendix IV and Appendix V)

4.2 Radiation Therapy (Total pelvic field)

4.21 Physical Factors

A cobalt ⁶⁰ supervoltage unit or linear accelerator with an energy of 4 MeV or greater may be used. The minimum source to skin distance (SSD) or target to skin distance (TSD) is 80 cm with a minimum dose rate of 40 cGy/minute at 80 cm. Interstitial therapy is not acceptable in this protocol.

4.22 Localization and Simulation Methods

Localization films taken on the simulator and/or the treatment machine will be necessary in all cases. Polaroid pictures of all treatment portals with the patient in the treatment position are required.

4.23 Treatment Plan, Dose Specifications and Distribution

The patient may be treated with AP and PA parallel ports with each port being treated each day beginning no later than 8 weeks after surgery. A four field box technique with parallel opposed AP/PA two opposing lateral fields may be used in patients requiring TPR.

4.231 Daily Tumor Dose, Total Dose and Overall Treatment Time

A daily tumor dose of 180 cGy per day will be given to a total dose of 5040 cGy (180 x 28 treatments) in approximately six weeks.

4.232 Dose Distribution: Site

The tumor dose should be calculated at the midplane on the central axis and the dose within the entire field should not vary more than 5%. The dose distribution in the pelvis should deliver not less than 5040 cGy to a point 7 cm lateral to the midline of the pelvis at the widest transverse diameter of the pelvis (point P).

4.24 Portal and Treatment Volume Definition

The volume irradiated in the total pelvis port should include the following: the upper one-half of the vagina, the paracervical, the parametrial and the uterosacral tissues as well as the external iliac. The hypogastric, and the obturator nodes should be included in the treatment port.

This volume should have the following boundaries:

4.241 Total Pelvic Fields

Superior border: A transverse line drawn through the L4-L5 interspace.

Inferior border: The mid-portion of the obturator foramen.

Lateral borders: One cm beyond the lateral margins of the bony pelvic wall at the widest plane of the pelvis (this must be at least 7 cm from the midline in this plane).

4.242 Lateral Pelvic Fields

Superior border: A vertical line drawn through the L4-L5 interspace which matches the superior margin of the AP/PA ports.

Inferior border: A vertical line of the AP/PA ports which matches the inferior margins of the AP/PA ports.

Anterior border: A horizontal line drawn just anterior to the symphysis pubis with an adequate margin to ensure inclusion of lymph nodes above the vertebral bodies.

Posterior border: A horizontal line at the posterior border of the 3rd sacral vertebra which is parallel to the anterior border of the lateral pelvic field. (The anterior-posterior dimension of the lateral fields should be a minimum of 9 cm.)

4.25 Blocking and Normal Tissue Sparing

No pelvic organs or structures may be blocked during total pelvic radiation.

4.26 Treatment Schedule

4.261 Technique: Both parallel opposed AP/PA fields will be treated each day. When lateral pelvic fields are used during box field radiation each lateral opposed port will be treated each day. AP/PA paired fields and lateral fields may be alternated every other day.

4.262 Fractionation: Daily treatments will be given with five fractions per week.

4.263 Therapy Interruptions:

4.2631 If interruption of two weeks or less occurs, radiation should be completed to the prescribed total dose.

4.2632 When therapy interruptions of more than two weeks occur, this will be considered a major deviation from the protocol and resumption of therapy will be at the discretion of the radiation oncologist. Follow-up must continue regardless of radiation treatment received.

4.27 Expected Toxicity

Toxicity will vary depending upon tolerance of individual patient, daily dose, total dose, overall treatment time, associated illness, etc. The following toxicity criteria may be used.

4.271 Gastrointestinal

Nausea and vomiting is unusual, but may be seen after pelvic radiation. Antiemetics may be used during treatment or may be given prophylactically the night prior to treatment. Intractable nausea or vomiting is rarely seen with pelvic radiation alone and is usually the result of another process i.e., bowel obstruction. Increased bowel activity with diarrhea usually can be controlled with low fiber, low fat, bland diets and anti-diarrhea medications. Should G.I. toxicity become severe, hospitalization may be required at which time the treatment is interrupted temporarily until the patient's condition improves.

4.272 Hematological

Hematological toxicity is infrequently seen unless pelvic radiation is accompanied by chemotherapy. A CBC should be obtained weekly, and if WBC falls below 2000 or the platelet count drops below 100,000, counts should be obtained twice weekly.

4.28 Radiation Therapy Quality Control and Documentation

The Radiologic Physics Center, under the sponsorship of the American Association of Physicists in Medicine, will supervise the dosimetry control for this clinical trial. To participate in the trial, the institutions must demonstrate the ability to achieve an accuracy of $\pm 3\%$ measuring the output of their sources and $\pm 5\%$ in delivering the prescribed dose.

The American College of Radiology will review pretreatment films, calculations, and plan of treatment (Rapid Turnaround).

The following information will be needed for this review:

- One copy each of simulator and verification films
- Stage of disease
- Plan of treatment (dose prescription)
- Initial calculations
- Representative film of initial field

4.3 Pathologic Evaluation

4.31 The uterus will be evaluated in regard to:

1. Location of tumor in uterus or cervix.
2. Depth of myometrial invasion.
3. Differentiation/Grade of tumor.
4. Size of uterus.
5. Histologic type of tumor.