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PROTOCOL GOG #122

~~CIRCADIAN-TIMED~~ **WHOLE ABDOMINAL RADIOTHERAPY VERSUS
COMBINATION DOXORUBICIN-CISPLATIN
CHEMOTHERAPY IN ADVANCED ENDOMETRIAL CARCINOMA**

(PHASE III)

(POINTS - 6)

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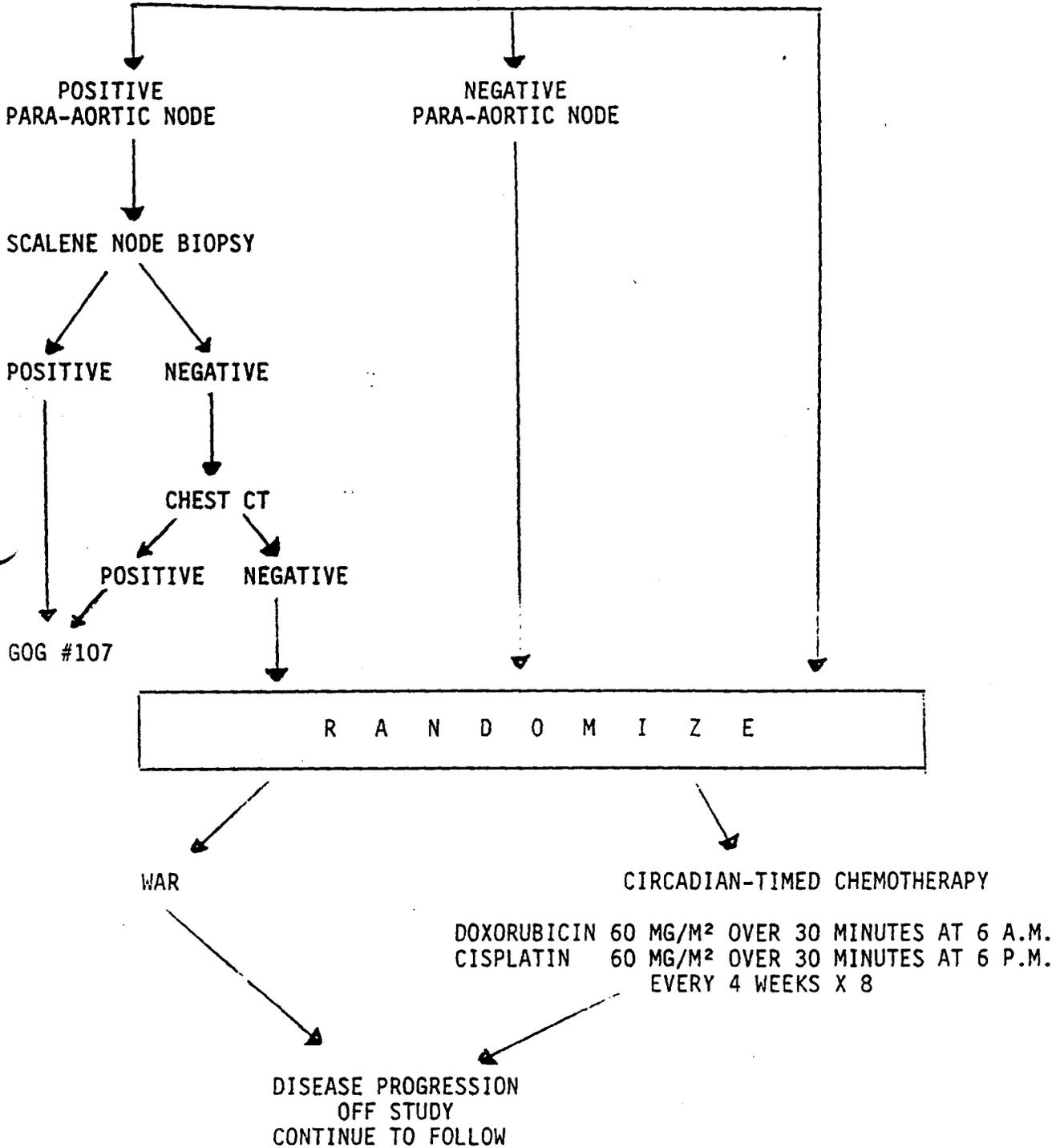
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S C H E M A

SURGICAL STAGE III/IV ENDOMETRIAL CARCINOMA, \leq 2 CM RESIDUAL
(DISTANT METASTASIS EXCLUDED)

TAH/BSO
PAN SAMPLING OPTIONAL



1.0 OBJECTIVES

- 1.1 To compare treatment outcomes (survival and progression-free interval) and failure patterns in patients with stages III-IV endometrial carcinoma (≤ 2 cm residual disease) treated with whole abdominal irradiation versus circadian-timed combination doxorubicin-cisplatin chemotherapy.
- 1.2 To determine and compare the incidence and type of acute and late adverse events observed with the two treatment regimens.

2.0 BACKGROUND AND RATIONALE

Although localized endometrial cancer is effectively treated using surgery and radiation therapy, treatment of advanced endometrial cancer remains problematic. The American Cancer Society estimates that 5500 women will die of this disease in 1991.[1]

The optimum adjuvant therapy following surgical staging and maximum cytoreduction is unknown. The Gynecologic Oncology Group has evaluated medroxy-progesterone acetate (50 mg po tid), finding an overall response rate of 14%. Well differentiated tumors responded better than poorly differentiated tumors. Since 92% of stage III patients have moderate to poorly differentiated lesions, expected response to progestins is poor in patients with advanced disease.[2]

Systemic chemotherapy has been similarly disappointing when given to patients with advanced or recurrent endometrial cancer. In GOG protocol #48, only 25.3% of patients receiving doxorubicin +/- cyclophosphamide responded to therapy (10.4% CR).[3] In GOG protocol #26-C, 56 patients treated first-line with single-agent cisplatin (50 mg/m²) demonstrated a complete response rate of only 4%.[4]

Whole abdominal radiation (WAR) has been suggested as an adjunctive treatment in patients with stages III and IV endometrial carcinoma. Potish et al reports disappointing results treating patients with intra-abdominal metastases with WAR.[5] Based on a retrospective analysis of failure patterns in clinical and surgical stage III patients, Greven et al concluded that the high rate of distant metastasis precludes a significant impact on survival by WAR.[6] However, Greer and Hamberger reported more promising results in patients with small residual disease (< 2 cm) treated with WAR using a moving strip and pelvic boost. Twenty-seven patients had an absolute survival of 63% with acceptable rates of acute and late complications.[7] Similar favorable results were reported by Martinez et al who observed 5 year relapse-free survivals of 78% and 53% in patients with stages III and IV disease, respectively.[8] In GOG protocol #94, a phase II study, WAR was prospectively evaluated. Although data analysis from this study is incomplete, it appears that the WAR regimen employed is tolerable with some evidence of efficacy.

In protocol #96, the GOG evaluated circadian-timed combination doxorubicin cisplatin chemotherapy in advanced and recurrent endometrial cancer, finding a 60% response rate in 30 evaluable patients.[9] This high response rate is consistent with previous observations that circadian scheduling of chemotherapy may improve response rates and median survivals and lessen toxicity.[10, 11]

Based on these previous GOG studies, we propose to compare directly, in randomized fashion, WAR and circadian-timed doxorubicin-cisplatin in patients with stages III and IV endometrial cancer to determine the regimen with the most promise as a surgical adjuvant.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

- 3.11 All patients with advanced endometrial carcinoma, of any histology including clear cell and serous papillary carcinomas.
- Surgical stage III and IV disease, including those patients with positive adnexa, tumor invading the serosa, positive pelvic and/or para-aortic nodes, involvement of bowel mucosa, intra-abdominal metastases, positive pelvic washings or vaginal involvement within the radiation port. (Appendix III)
- 3.12 Surgery must have included a total abdominal hysterectomy, and bilateral salpingo-oophorectomy. Selective pelvic and para-aortic lymph node sampling is optional. Radiotherapy (RT) and chemotherapy will be initiated within 8 weeks after surgery.
- 3.13 Tumor must be maximally debulked to 2 cm or less.
- 3.14 All positive para-aortic node patients are to be further staged by scalene node biopsy and chest CT scan. If both are negative, patients are eligible.
- 3.15 Prior therapy with progestational agents is permissible (this is the only form of therapy other than surgery which is permissible).
- 3.16 All patients and/or guardians must have signed an informed consent prior to entry into the study.
- 3.17 Patients who have met the pre-entry requirements specified in Section 7.0.

3.2 Ineligible Patients

- 3.21 Patients with recurrent disease.
- 3.22 Patients with residual tumor after surgery (any single site) exceeding 2 cm in maximum dimension.
- 3.23 Patients with:
- a. parenchymal liver metastasis
 - b. lung metastasis
 - c. positive inguinal lymph nodes
 - d. positive scalene nodes
- 3.24 Patients who have had pelvic or abdominal radiation therapy.

- 3.25 Patients who have had prior chemotherapy.
- 3.26 Patients with inadequate hematologic, renal or hepatic function:
WBC < 3,000; platelets < 100,000; granulocytes < 1,500;
creatinine > 2.0 mg%; bilirubin, SGOT > 2x normal.
- 3.27 Patients with GOG Performance Grade of 4.
- 3.28 Patients with past or concomitant malignancy other than skin
(excluding melanoma).

4.0 STUDY MODALITIES

4.1 Surgery

- 4.11 An abdominal incision will be made to adequately explore the total abdomen so as to satisfy the protocol requirements.
- 4.12 The volume of any free peritoneal fluid should be estimated and described in the operative note. Free peritoneal fluid is to be aspirated for cytology. If no free peritoneal fluid is present, then peritoneal saline washings should be obtained from the pelvis.
- 4.13 The serosa of the entire gastrointestinal tract should be visually and palpably inspected.
- 4.14 Careful inspection of the omentum and removal of sections of omentum with gross masses should be performed when technically possible.
- 4.15 Removal of all resectable gross tumor in the above procedure is accomplished.
- 4.16 Pelvic and para-aortic node sampling is optional for patients with stage III or IV disease by other criteria.
- 4.17 Total abdominal hysterectomy and bilateral salpingo-oophorectomy of the extra-fascial type is performed. (See Appendix IV)
- 4.18 If positive para-aortic nodes, scalene node biopsy must be negative.

4.2 Radiation Therapy

Patients randomized to receive radiation therapy will have therapy initiated within eight weeks after surgery.

4.21 Physical Factors

All treatment will be delivered by megavoltage equipment ranging from 6 to a maximum of 25 MeV photons. The minimum source skin distance (SSD) will be 80 cm, dose rates between 30 and 200 cGy per minute at the midplane of the patient may be used. Cobalt-60 equipment will not be acceptable for treatment in this protocol.

4.22 Localization and Simulation Methods

Localization films taken on the simulator will be necessary in all cases. If fluoroscopic visualization of diaphragm movement is not possible, localization films demonstrating adequate coverage of the diaphragm should be taken at the time of patient's quiet expiration. Polaroid pictures of all portals with the patient in the treatment position are required.

4.23 Treatment Plan and Dose Specification

All doses will be calculated at the midplane in the center of the target volume for opposed fields and at isocenter for multiple field arrangements (four-field).

4.231 Whole Abdominal Irradiation

Initially, the whole abdomen will be treated. The whole abdomen is to be irradiated with opposed fields to a total dose of 3000 cGy in 20 fractions of 150 cGy each. Should the treatment not be tolerated because of GI symptoms or leukopenia, the daily fraction may be decreased to 125 cGy per day. Five half value layer kidney shields will be used in the PA field throughout treatment of the abdomen. No liver shielding is employed.

Abdominal field borders for RT planning are as follows:
- Inferior borders - inferior border of obturator foramina;
- superior border - one centimeter above the dome of the diaphragm at the patient's maximum comfortable expiration;
- lateral borders - one centimeter lateral to the widest point of the peritoneal fat stripe and/or beyond the laterally visualized intestine. This may or may not extend to be tangential on the lateral abdominal wall.

It will usually be possible to shield a portion of the lung base and heart and still maintain a one centimeter margin above the left hemidiaphragm.

Shielding of the field corners is encouraged.

Kidney shields 5 HVL thick will be used in the PA field throughout treatment of the abdomen. IVP or CT scans should be used to aid in kidney block placement.

4.232 Para-aortic and/or true pelvic boost

Patients with positive pelvic and/or para-aortic lymph nodes and patients not undergoing pelvic and para-aortic lymph nodes sampling will receive a boost to both areas. Other patients will receive boosts to true pelvis only. An isocenter dose of 1500 cGy in eight fractions will be delivered.

A four-field box technique is mandatory for inclusion in this protocol. In an effort to reduce toxicity, it is highly recommended that each patient swallow a dilute solution of an appropriate contrast material approximately 30 minutes before simulation so that the small bowel can be identified on the simulator films. The use of individualized custom blocking is highly recommended.

The true pelvis boost will be arranged as follows:

Cephalad Border:

A transverse line drawn through the S1, S2 inter space.

Caudal Border:

The mid portion of the obturator foramen or the lowest extension of suspected disease with a minimum of 2 cm margin.

Lateral Borders:

1 cm beyond the lateral margin of the true pelvis at its widest points.

Lateral Pelvic Fields:

The cephalad and caudal borders are as above.

Anterior Border:

A horizontal line drawn through the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to known nodes or in the absence of radiographic documentation, the line should pass at least 1.5 cm anterior to the lumbar vertebral bodies. Individualized custom blocks can be used to achieve this goal.

Posterior Border:

A horizontal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3 cm. Surgical clips that are known to mark sites of lymph node removal should always be included.

Periaortic Fields

A four-field arrangement for para-aortic irradiation is mandatory. At the discretion of the treating radiation therapist, the periaortic fields and pelvic fields can be combined into a single large "spade" arrangement. If the option of separate fields is chosen, then an appropriate gap calculation should be made.

AP/PA Fields:

Cephalad Border:

A transverse line drawn at the T11 and T12 inter space.

Caudal Border: The mid-portion of the obturator foramen or the lowest extension of suspected disease with a minimum of 2 cm margin.

AP/PA Lateral Borders:

If radiographic evidence is available, the field should include all lymph nodes with at least a 1 cm margin. In the absence of such evidence, the minimum width will be 5 cm and it is suggested that the borders pass through the tips of the lumbar transverse processes.

Periaortic Lateral Fields

It is necessary to document the location of the kidneys via a CT scan or IVP. Under no circumstances should more than 1/3 of each kidney be included in the treatment volume.

The cephalad and caudal borders are as above.

Anterior:

The anterior border should encompass all known lymph nodes with a margin of 1 cm. In the absence of radiographic documentation, it is recommended that this border be at least 2 cm anterior to the vertebral bodies.

Posterior:

The posterior border will be defined by an individualized custom block in conjunction with the primary collimators. The ultimate result is that the spinal cord should be shielded throughout entire length with a margin of at least 0.5 cm.

Separate isodose distributions through the para-aortic and pelvic portions of the pelvic and para-aortic portals should be obtained and submitted for review.

4.24 Treatment Schedule

4.241 All fields are treated with each fraction, treating once per day, 5 days per week.

4.242 Therapy Interruptions

- 4.2421 If interruption of therapy up to two weeks becomes necessary, radiation should be completed to the prescribed doses.
- 4.2422 If more than two weeks interruption is required, the patient will be taken off study. Resumption of therapy is at the discretion of the radiation oncologist. Follow-up will continue regardless of treatment.

4.25 Expected Toxicity

Common Toxicity Criteria are given in Appendix I.

- 4.251 Gastrointestinal: Nausea and vomiting may occur after whole abdominal treatments, especially after each of the first few doses. Patients may be pre-treated with an appropriate antiemetic. Intractable nausea and vomiting beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is rarely seen as a result of radiation alone.

Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic radiation. It is recommended that instructions be given to patients for low fiber, low fat, bland diet. Most patients will require antidiarrheal medications such as diphenoxylate HCL with atropine sulfate (Lomotil) or loperamide HCL to control diarrhea.

Should GI toxicity become severe enough to require hospitalization for IV fluid replacement, treatment should be discontinued temporarily until the patient's condition improves.

- 4.252 Hematologic toxicity of a mild nature will be seen frequently with a decline in WBC and platelet count.
- 4.253 Hepatic toxicity should rarely occur. When seen, it will usually appear as marked fatigue usually without other symptoms. Elevations of alkaline phosphatase, SGOT and/or bilirubin may occur.

4.26 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 $\pm 3\%$ in measuring the output of their sources and $\pm 5\%$ in delivering the prescribed dose.