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PROTOCOL GOG #123

A RANDOMIZED COMPARISON OF RADIATION THERAPY & ADJUVANT HYSTERECTOMY
VERSUS RADIATION THERAPY AND WEEKLY CISPLATIN AND ADJUVANT HYSTERECTOMY
IN PATIENTS WITH BULKY STAGE IB CARCINOMA OF THE CERVIX

(PHASE III)

NAV1.954720.002

(POINTS - 6)

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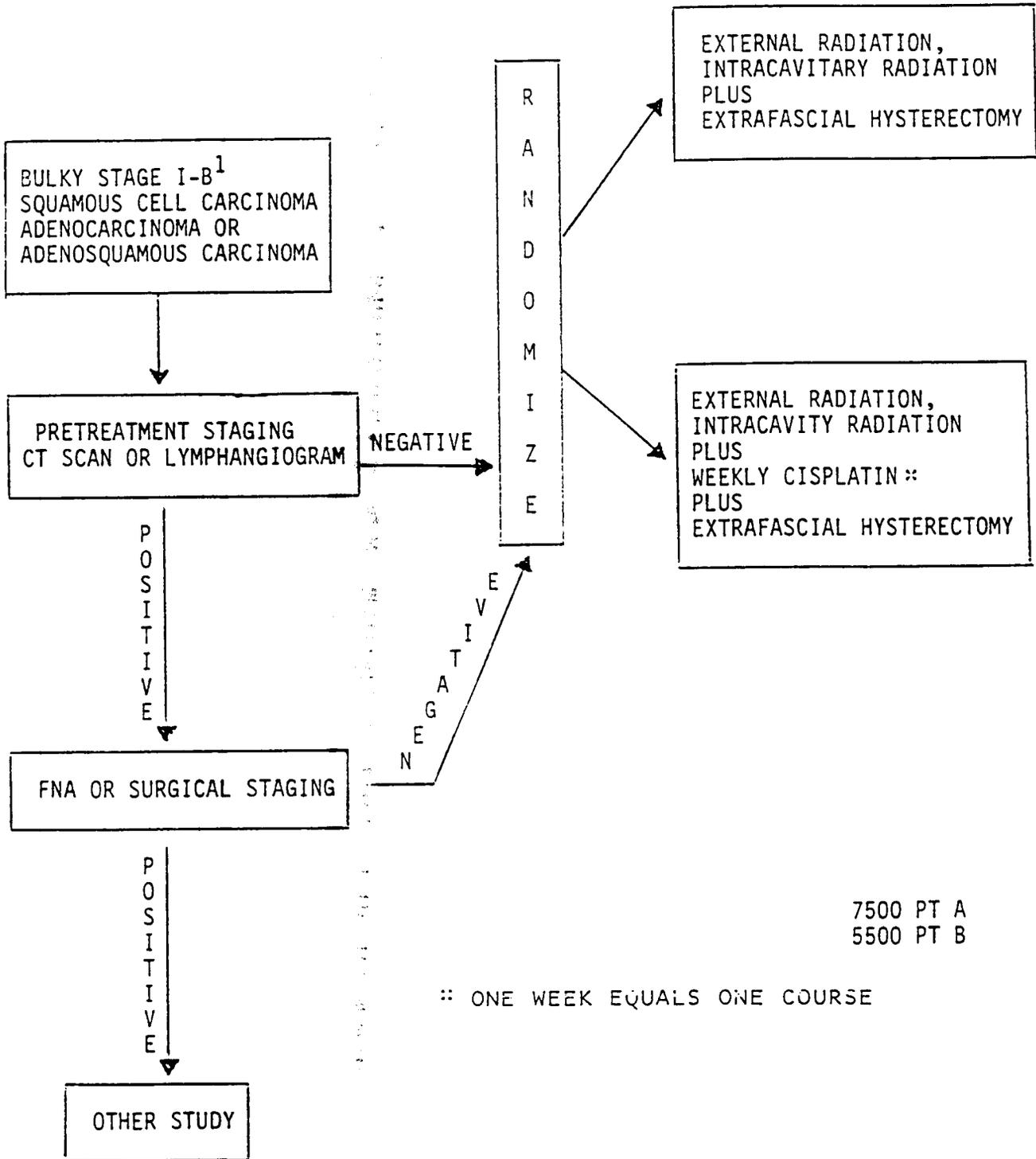
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OPEN TO PATIENT ENTRY FEBRUARY 24, 1992
REVISED MARCH 27, 1992
REVISED JULY 2, 1992
REVISED SEPTEMBER 11, 1992

S C H E M A



7500 PT A
5500 PT B

** ONE WEEK EQUALS ONE COURSE

1 Defined in section 3.11

1.0 OBJECTIVES

- 1.1 To determine if weekly cisplatin infusion improves local regional control and survival when added to radiation therapy plus extrafascial hysterectomy.
- 1.2 To determine the relative toxicities of these two treatment arms.

2.0 BACKGROUND AND RATIONALE

Tumor volume is one of the most important prognostic factors in all human malignancies and certainly cervical carcinoma is no exception.[1] The clinical staging system used by the M.D. Anderson Hospital in Houston, Texas for cervical carcinoma, in fact, is based on the combination of extent of tumor spread and size of tumor.[2] Within each of the FIGO Stages of disease larger and more extensive tumors carry a higher failure rate and are more difficult to treat with whatever modality is used. In Stage IB cervical carcinoma larger or bulky tumors, including those described as "barrel shaped", are demonstrably more difficult to cure with primary surgical treatment.[3] The use of radiation therapy for Stage IB carcinoma of the cervix is generally effective but has a poorer track record in providing central disease control within the primary site itself. Thus there has developed considerable literature supporting the concept of adjuvant hysterectomy after radiation therapy in large cervical carcinomas.[4] The role of this adjuvant hysterectomy approach is being tested in current GOG Protocol #71 in a randomized comparison with standard radiation therapy alone.[5]

Preliminary data from Protocol #71 indicates a fairly probable outcome of increased local control in the combined radiation/adjuvant hysterectomy treatment arm with uncertain effect on survival at this point.[5]

There is accumulating experience with the use of radiation in combination with cisplatin alone or cisplatin and other drug combinations. Current GOG Protocol #85 compares radiation plus Hydroxyurea vs. radiation plus cisplatin/5FU infusion therapy for locally advanced cervical carcinoma.[6] This protocol has demonstrated acceptable toxicity for this combination treatment approach and at least a suggestion of more rapid tumor response with uncertain effect on ultimate local tumor control. Another approach that has been used by a number of investigators at Roswell Park,[7] University of Minnesota,[8] and Albany Medical College,[9] includes the use of weekly cisplatin infusion with conventional fractionated radiation therapy in extensive disease. Again both published reports and unpublished experience have indicated good tolerance and response in patients with cervical carcinoma. GOG patients with positive para-aortic nodal metastases have experienced no relapses in either their pelvic disease or in the para-aortic areas.[9]

In this study we to compare the addition of weekly cisplatin infusion with the current apparent better arm of Protocol #71: radiation therapy plus adjuvant hysterectomy in patients with bulky Stage IB carcinoma of the cervix. The rationale for the use of cisplatin is the combination of its effect as the single most effective drug currently available for use in squamous cell carcinoma of the cervix and its demonstrated radiation sensitizing effect. The use of a weekly program during external and intracavitary radiation therapy should accentuate its radiation sensitizing effects and may be responsible for the high rate of local control seen in relatively small numbers of patients treated thus far.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

- 3.11 Patients with primary, previously untreated, histologically confirmed invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix Stage IB who have large bulky lesions as follows:
 - 3.111 Lesions \geq 4 cm
 - 3.112 Barrel shaped lesions
- 3.12 Pelvic and/or para-aortic lymph nodes must be radiographically or surgically negative. If CT scan or lymphangiogram is positive or suspicious, fine needle aspiration (FNA) cytology or histological confirmation of pelvic and/or para-aortic nodes must be negative.
- 3.13 Patients with adequate bone marrow function: WBC equal to or greater than 3,000 per ml; platelets equal to or greater than 100,000 per ml.
- 3.14 Patients with adequate renal function: creatine equal to or less than 2.0 mg percent.
- 3.15 Patients with adequate hepatic function: bilirubin, and SGOT equal to or less than two times normal.
- 3.16 Patients who have met the pre-entry requirements specified in Section 7.0.
- 3.17 Patients who have signed an approved informed consent.
- 3.18 Patients must be entered within eight weeks of diagnosis.

3.2 Ineligible Patients

- 3.21 Patients with recurrent carcinoma of the uterine cervix regardless of previous treatment, or cancers other than squamous cell, adeno-squamous or adenocarcinoma.
- 3.22 Patients who have not been or cannot be adequately clinically staged.
- 3.23 Patients who had any previous pelvic radiation or have received systemic chemotherapy.
- 3.24 Patients whose circumstances will not permit completion of the study or required follow-up.
- 3.25 Patients with GOG performance status of grade 4.
- 3.26 Patients with previous or concomitant other malignancies except non-melanoma skin cancers.

3.27 Patients with histologically confirmed malignancy outside of the cervix.

3.28 Patients with previous partial or total hysterectomy.

3.29 Patients who are deemed medically inoperable.

4.0 STUDY MODALITIES

All eligible patients will undergo clinical staging as permitted by the FIGO rules (Appendix III). It will be optional for patients to undergo pre-randomization surgical staging to include extraperitoneal sampling of pelvic and/or para-aortic lymph nodes (Surgical Procedures Manual, Appendix IV).

4.1 Pre-operative Clinical Staging

Patients will have a chest x-ray and an abdominal pelvic CT scan with intravenous contrast. IVP and lymphangiogram are optional. Pelvic examination is required. Cystoscopy and sigmoidoscopy are to be performed when clinically indicated.

4.2 Surgical Procedures

4.21 Surgical Staging

Extra peritoneal pelvic and/or para-aortic node sampling is optional (see schema). These patients can be staged in a manner similar to that performed for Stage IIB - IV cervical carcinoma. Pelvic nodes below the mid common iliac area need not be sampled.

4.22 Extrafascial hysterectomy, adnexectomy and intra-abdominal exploration will be performed 3 to 6 weeks following completion of the radiation therapy. The surgical procedure is outlined in Appendix V.

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4.3 Radiation Therapy Procedures

Radiation therapy should be started within two weeks of randomization.

4.31 Radiation therapy is identical in both regimens.

4.311 External Radiation

Patients will receive 4500 cGy external beam therapy delivered homogeneously to the pelvis in 4-5 weeks. (See Section 4.33 for dose distribution. Five day/week fractions of 180-200 cGy)

NOTE: If after 4500 cGy it is not possible to deliver adequate intracavitary treatment, external treatment may be continued up to a maximum of 5000 cGy in 5-6 weeks, then intracavitary treatment will be delivered.

4.312 Intracavitary Irradiation

Either one or two intracavitary applications may be used to deliver 3000 cGy to Point A using standard after loading applicators with stem and ovoids.

If the external treatment has been carried to 5000 cGy (see 4.311) the intracavitary application should be modified to deliver 2500 cGy.

NOTE: If the external treatment is carried to 4500 cGy, the intracavitary dose will be 3000 cGy Point A dose, in order to achieve the prescribed 7500 cGy Point A dose total (combined external and intracavitary treatment).

4.313 Completion of Treatment

If necessary to raise the Point B dose to the prescribed 5500 cGy total dose level, additional external radiation with central shielding should be given after the intracavitary applications in order to accomplish this.

NOTE: All radiation therapy must be completed within 10 weeks of its initiation.

4.32 Dose distribution for both regimens: a four field pelvic block technique with opposing anterior and posterior and two opposing lateral fields will be used. Dose distribution across the treatment volume should not vary by more than 5% from the recommended dose. All fields must be treated each day.

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4.33 Radiation Sources

Radiation sources employed in these clinical trials will be x-ray generators which produce x-ray beams with a photon energy of 4 MeV or more, preferably with treatment distances of 100 cm or more.

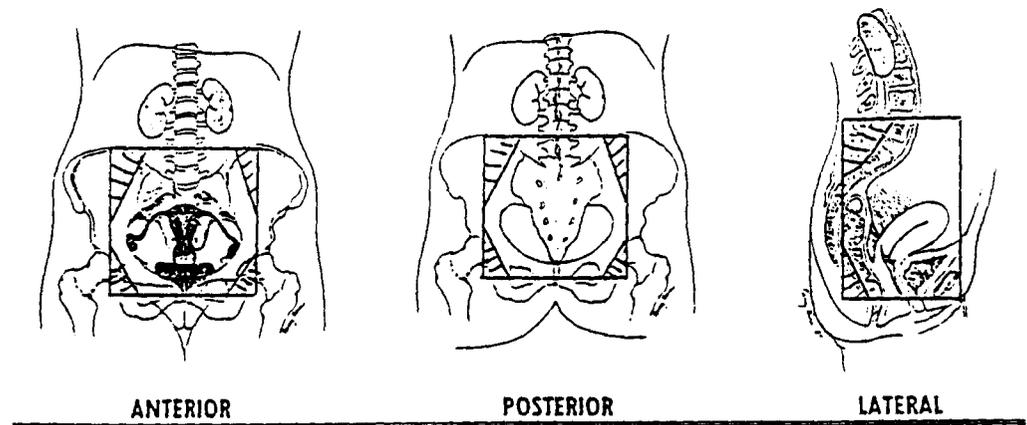
4.34 External Radiation Fields

Radiation field dimensions will follow the guidelines outlined in the Radiation Therapy Procedures Manual. The superior border will be through the L4/5 inter space. Lateral margins will be 1 cm or more beyond the lateral margins of the bony pelvis and the inferior border will be at the inferior border of the obturator foramen or below the lowest extension of disease with an adequate margin, whichever is the lowest.

For the lateral field the anterior field should be a horizontal line drawn at the anterior border of the symphysis pubis, and the posterior border should be a horizontal line drawn through the inferior anterior margin of S2. The superior inferior borders of the lateral fields will be at the same location as the anterior and posterior fields.

A four field technique will be used for all patients. Normal tissues not requiring treatment should be shielded where possible. The recommended blocking is shown in the field diagram.

Recommended Blocking Arrangement Field



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4.35 Required Materials Submission

GOG Forms G and I should be completed and submitted at the completion of therapy. They should be accompanied by copies of the simulation and portal verification films as well as copies of the implant localization films. A copy of the treatment record, treatment summary, dosimetry and calculations should also be submitted.

4.36 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.

4.4 Chemotherapy

4.41 Cisplatin (Platinol[®] - NSC #119875)

4.411 Formulation: Cisplatin is available as a dry powder supplied in 10 mg and 50 mg vials and in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride.

4.412 Preparation: The 10 mg and 50 mg vials should be reconstituted with 10 ml or 50 ml sterile water for injection, USP respectively. Each ml of the resulting solution will contain 1 mg of Platinol. Reconstitution as recommended results in a clear colorless solution.

NOTE: Aluminum reacts with Platinol causing precipitation formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Platinol.

Revised 9/11/92