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PROTOCOL GOG #71

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TREATMENT OF PATIENTS WITH SUB-OPTIMAL ("BULKY") STAGE IB
CARCINOMA OF THE CERVIX:
A RANDOMIZED COMPARISON OF RADIATION THERAPY
VERSUS
RADIATION THERAPY PLUS ADJUVANT EXTRAFASCIAL HYSTERECTOMY
(PHASE III)

GOG CATEGORY I - 6 CREDITS

PROTOCOL FORMAT: GOG

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ENCLOSURE (14)

S C H E M A

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A RANDOMIZED COMPARISON OF RADIATION THERAPY
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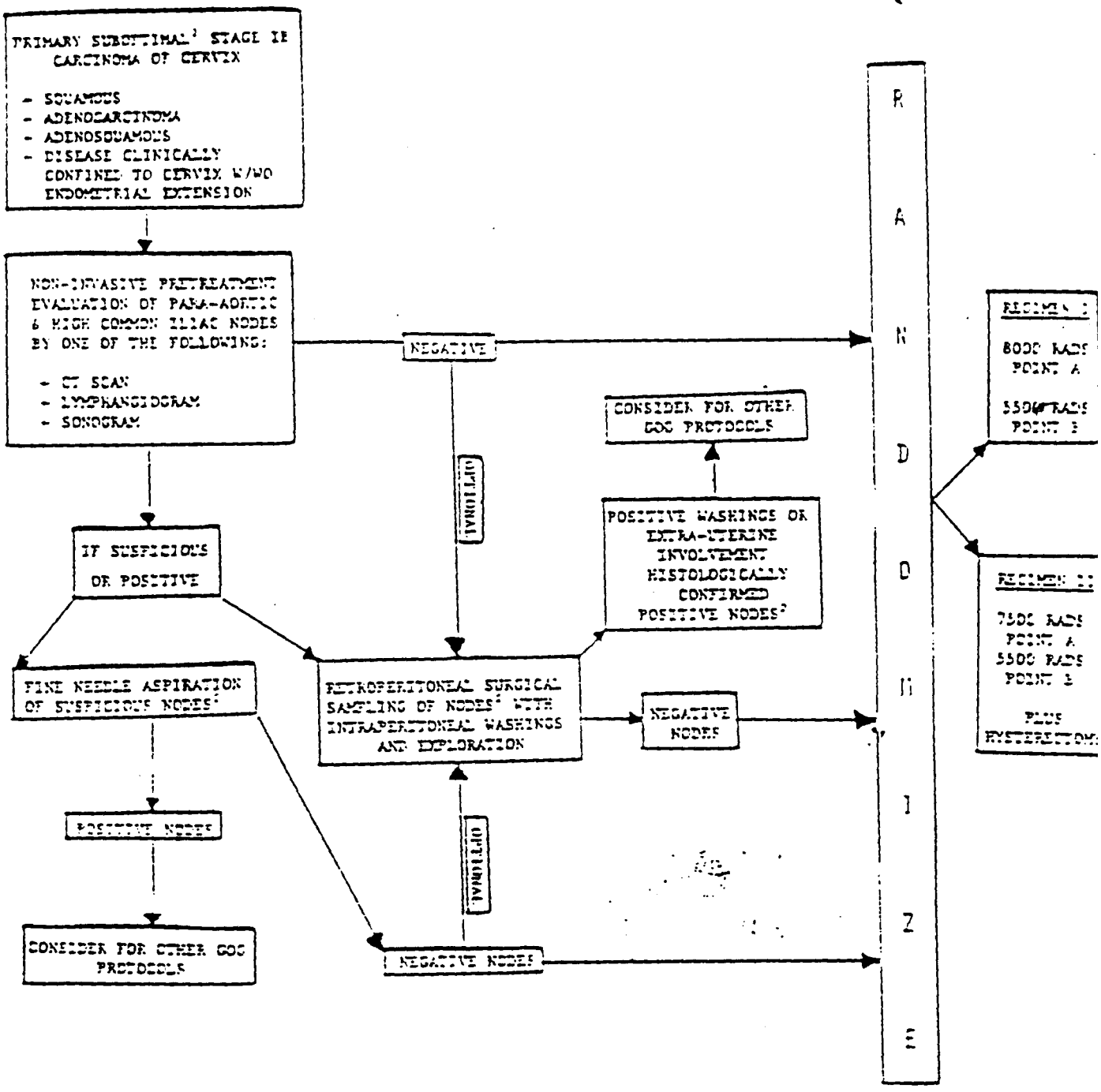

[1] SUBOPTIMAL DEFINED IN SECTION 3.13
[2] PARA-AORTIC AND/OR HIGH COMMON ILIAC NODES

Rev. 5/5/86

1.0 OBJECTIVES

1.1 Evaluation of the role of adjunctive extrafascial hysterectomy in the treatment of suboptimal Stage IB carcinoma of the cervix.

1.2 Evaluation of survival and patterns of failure in suboptimal IB cervix cancer.

1.3 The study of toxicity of a combined radiation and surgical therapeutic program.

1.4 Evaluation of the prognostic value of various surgical/pathological characteristics in suboptimal Stage IB carcinoma of the cervix.

2.0 BACKGROUND AND RATIONALE

Tumor volume is regarded to be the most important prognostic factor in most human cancers, and there is considerable evidence that this is true for carcinoma of the cervix. For the purposes of this protocol, the terms "suboptimal" or "bulky" are used to describe large volume, Stage IB cervical carcinomas. These occur in two anatomical forms: the exophytic cervix cancer grows out from the cervix toward the lower vagina, often acquiring considerable diameters; endophytic cancers, usually thought to arise in the endocervix and frequently adenocarcinomas, grow within the stroma of the cervix, expanding cervical tissue into the shape of an indurated cylinder, or a rain barrel. In such cases, the parametrium appears encroached upon, but actual nodular spread is not detected by the physician. Cure rates in suboptimal Stage IB cervix carcinoma are generally considered to be less than those found following treatment of smaller lesions. This is attributable to the higher rate of local, regional, and distant metastases as tumor volume increases.

Presumably, local failure relates to the relative radio-resistance of bulky tumors to intracavitary applications, due to physical principles derived from the inverse square law. Persistent local disease could be removed with adjunctive hysterectomy following radiation therapy. Regional and distant metastases may be occult in lymph nodes at the time of primary treatment, due to insufficient pre-invasive or invasive lymph node evaluation; in addition, documented metastases, particularly if they are larger than 1.5 to 2 centimeters, may not be sterilized by generally accepted levels of pelvic wall radiation in cervix cancer.

Considerable data have been generated regarding the role of adjunctive hysterectomy in the control of local disease following radiation therapy for the suboptimal, early stage malignancies of the cervix. Most of this material[1-7] is from the M.D. Anderson Hospital, and, while later publications support the use of adjunctive hysterectomy in reducing central recurrences, cure rates have not been affected. More recently, Rotman[8] questioned the use of adjunctive hysterectomy in bulky or barrel-shaped Stage IIB lesions, and noted a three-fold increase in fistulae and doubling in obstructive uropathy in patients treated with radiation plus radical surgery. Perez[9] studied 102 cases of Stage IB and IIA cancers (not limited to bulky or barrel-shaped lesions) and cases were equally divided between those treated with radiation therapy alone versus those treated with radiation therapy and radical hysterectomy with lymphadenectomy. No cases of IB disease failed locally, while three treated with combined therapy developed pelvic failures. The difference is probably not statistically significant, and Perez concluded that there was no significant difference in cure rates or morbidity between that group of patients treated with radiation alone versus those patients treated with radical hysterectomy and lymphadenectomy following radiation therapy. Additional publications do not further clarify these questions.[10-13]

For these reasons, it appears that the stage has been set for a large-scale cooperative group study in which suboptimal Stage IB cancers of the cervix could be studied in a prospective fashion. The Gynecologic Oncology Group could determine whether hysterectomy affects local control or cure rates, what the complication rates in a multi-center study would be, and what failure patterns exist.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients with primary, untreated, histologically confirmed invasive carcinoma of the uterine cervix (with or without endometrial extension), suboptimal or bulky (as defined in Section 3.13), FIGO Stage IB, as confirmed by cervical biopsy and endometrial sampling (biopsy or curettings), and studies specified in Section 7.0.

3.12 Patients with the following histologic types of cancer:

- Squamous carcinoma
- Adenocarcinoma
- Adenosquamous carcinoma

3.13 Patients with "suboptimal" or "bulky" cancers are defined as follows:

3.131 Exophytic lesions with an external tumor diameter of 4 cm or greater, as measured by calipers: OR

3.132 A cervix expanded to 4 cm or greater, and presumed by the clinician to be principally involved with cancer, resulting in such an expansion: cylindrical or "barrel-shaped" cancers.

3.14 Patients with disease limited to the cervix by clinical, radiographic and/or surgical examination(s).

3.15 Patients who have signed the Consent Form.

3.2 Ineligible Patients

3.21 Patients with past or concomitant cancer other than skin (except melanoma).

3.22 Patients with WBC <3,000/mcl or platelet count <100,000/mcl.

3.23 Patients with septicemia or severe infection.

3.24 Patients with intestinal obstruction or gastrointestinal bleeding.

3.25 Patients with cervix cancer who have received any previous surgery, radiation or chemotherapy for that cancer.

3.26 Patients with significant impairment of hepatic function: alkaline phosphatase, SGOT, or bilirubin levels which are 2 x normal or higher. Patients with impairment of renal function: creatinine 2.0 or greater.

3.27 Patients whose circumstances will not permit completion of the study or the required follow-up.

3.28 Patients with renal abnormalities requiring modification of radiation fields (pelvic kidney, renal transplantation, etc.).

3.29 Patients with a ECG Performance Grade of 4.

3.30 Patients who are considered medically inoperable.

3.31 Patients with prior hysterectomy (total or subtotal).

3.32 Patients with radiographic or histologic involvement of the high common iliac or para-aortic lymph nodes, and patients who have other evidence of extrapelvic disease, including positive peritoneal cytology.

3.33 Patients who demonstrate metastasis to any extra-uterine site, other than pelvic nodes below high common iliac nodes.

4.0 STUDY PROCEDURES

4.1 Clinical Staging Evaluation

4.11 All patients with suboptimal Stage IB carcinoma of the cervix will have routine clinical evaluation, including history and physical examination and blood studies (CBC, differential, platelet count, creatinine, SGOT, alkaline phosphatase and bilirubin). All patients will have confirmation of diagnosis by cervical biopsy and endometrial sampling (biopsy or curettage). Chest x-ray and evaluation of the urinary tract (intravenous pyelography, radioisotopic renal scan or CT scanning with contrast) are required. The patient's disease must meet the criteria for clinical Stage IB (Appendix II).

4.12 Patients must be subjected to noninvasive pretreatment evaluation of the para-aortic nodes by one of the following: CT scan, lymphangiogram or sonogram. If in the pre-entry evaluation the patient had a CT scanning with contrast that included the para-aortic and high common iliac nodes in the study volume, this study will satisfy the requirement. If nodes are interpreted as suspicious or positive on the basis of the noninvasive evaluation, the investigator must proceed to do either fine needle aspiration for positive nodes or extra-peritoneal surgical sampling of nodes. If fine needle aspiration is negative or if the noninvasive evaluation is negative, extraperitoneal surgical sampling is optional.

4.2 Surgical Staging Procedure

4.21 Nodal Surgery

Patients may be evaluated surgically in the same way patients with Stage II, III and IVA cancers of the cervix are managed. The patient may undergo extraperitoneal surgical sampling of para-aortic and high common iliac nodes bilaterally as the first step (see Appendix IV). Pelvic lymph nodes below the level of the upper common iliac chain need not be sampled. Intraperitoneal exploration will be carried out after the retroperitoneal biopsies. Cytologic washings of the pelvic cavity must be obtained. Inspection of all intra-abdominal organs for evidence of metastases must be done and suspicious areas discovered should be biopsied, if possible. Handling of tissues in areas that will receive radiation subsequently should be minimal. The results of this surgical staging will then serve to determine whether patients will be eligible for this protocol. Those individuals meeting the eligibility requirements of Section 3.1 should be entered.

4.3 Required Pathology Material

Representative stained slides showing documentation of invasive cancer, as well as a slide from each additional biopsied positive site, including curettings, must be sent to the Operations Office with Form F (Pathology Form) and four copies of the dictated pathology report from the participating institution. The pathologist must specify histologic grade and type, location of all positive lymph nodes, and sites of lymph nodes removed. The total number of lymph nodes submitted should be recorded.

4.4 Radiotherapy Procedures

4.41 Regimen I. Radiation Therapy Only - Point A Dose 8000 cGy
Point B Dose 5500 cGy

4.411 External Irradiation

Patients will receive 4000 cGy external beam therapy delivered homogeneously to the pelvis in 4-5 weeks. (See Section 4.43 for dose distribution. 5 day/week fractions of 180-200 cGy).

NOTE: If after 4000 cGy it is not possible to deliver adequate intracavitary treatment, external treatment may be continued up to a maximum of 5000 cGy in 5 to 6 weeks, then intracavitary treatment will be delivered.

4.412 Intracavitary Irradiation in Two or One Applications

Patients will receive sufficient intracavitary treatment to raise the Point A doses to 8000 cGy minimum total (combined external and intracavitary treatment). Standard after loading stem and ovoid applicators should be used for this.

NOTE: If the patient received 4000 cGy Point A dose from external treatment, two 2000 cGy intracavitary applications would be used: if 5000 cGy external dose was given, then a single 3000 cGy application would suffice.

4.413 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 application in order to accomplish this.

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

4.42 Regimen II. Radiation Plus Hysterectomy
Point A Dose 7500 cGy
Point B Dose 5500 cGy

4.421 External Irradiation

Patients will receive 4500 cGy external beam therapy delivered homogeneously to the pelvis in 4 to 5 weeks. (See Section 4.43 for dose distribution. 5 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 to 6 weeks, then intracavitary treatment will be delivered.

4.422 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.

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).

4.423 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.

4.43 Dose Distribution

The dose distribution across the treatment volume should not vary more than 5% from the recommended dose.

4.44 Radiation Sources

Radiation sources employed in these clinical trials will be x-ray generators which produce x-ray beams with the peak photon energy of 4 MEV or more, or Cobalt 60 irradiators. Radiation output of the unit must be adequate to permit employment of a TSD or SSD of 80 cm or more.

Intracavitary radiation may be delivered by radium, cesium, or cobalt sources in standard or commonly used applicators, provided that acceptable radium dosimetry can be determined. Interstitial therapy is not acceptable for this protocol.

4.45 The volume irradiated will include the totality of the obvious disease, the whole uterus, paracervical, parametrial and uterosacral regions, as well as the areas of the external iliac, hypogastric and obturator lymph nodes. As a minimum, this volume would have the following boundaries:

Superior: The upper margin of L-5.

Inferior: The midportion of the obturator foramen, or the lowest extension of the disease with adequate margin.

Lateral: 1 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 of this plane).

4.46 Beam verification films will be obtained and submitted to the GOG Operations Office with the patient's records.

Orthogonal dosimetry films will be taken following the intracavitary insertion, and the film and calculations submitted to the Operations Office with the patient's records.