

# 88-002



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PROTOCOL GOG #88

A RANDOMIZED STUDY OF  
RADICAL VULVECTOMY AND BILATERAL GROIN DISSECTION  
VERSUS  
RADICAL VULVECTOMY AND BILATERAL GROIN RADIATION  
PHASE III

CATEGORY I -- CREDITS

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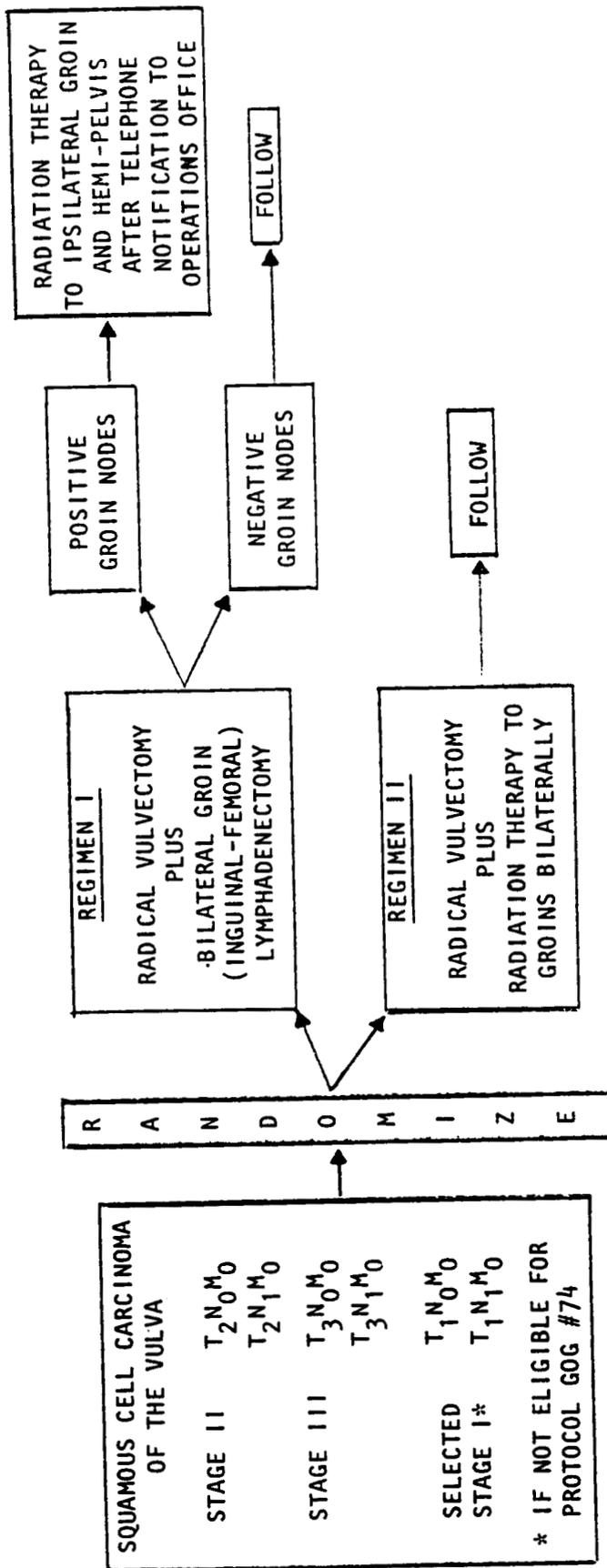
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S C H E M A

A RANDOMIZED STUDY OF  
 RADICAL VULVECTOMY AND BILATERAL GROIN DISSECTION  
 VERSUS  
 RADICAL VULVECTOMY AND BILATERAL GROIN RADIATION



SQUAMOUS CELL CARCINOMA OF THE VULVA

STAGE II    T<sub>2</sub>N<sub>0</sub>M<sub>0</sub>  
           T<sub>2</sub>N<sub>1</sub>M<sub>0</sub>

STAGE III    T<sub>3</sub>N<sub>0</sub>M<sub>0</sub>  
               T<sub>3</sub>N<sub>1</sub>M<sub>0</sub>

SELECTED STAGE I\*    T<sub>1</sub>N<sub>0</sub>M<sub>0</sub>  
                           T<sub>1</sub>N<sub>1</sub>M<sub>0</sub>

\* IF NOT ELIGIBLE FOR PROTOCOL GOG #74

NOTE: STAGE I PATIENTS MAY BE TREATED BY MODIFIED RADICAL HEMIVULVECTOMY AT DISCRETION OF TREATING PHYSICIAN.

EXCLUDE: T<sub>1</sub>N<sub>0</sub>M<sub>0</sub> } IF ELIGIBLE  
           T<sub>1</sub>N<sub>1</sub>M<sub>0</sub> } FOR GOG #74

T<sub>4</sub> LESIONS  
 N<sub>2</sub> OR N<sub>3</sub> LESIONS -- PATIENTS WITH SUSPICIOUS ENLARGED LYMPH NODES ARE NOT ELIGIBLE.  
 M<sub>1</sub> LESIONS

## 1.0 OBJECTIVES

- 1.1 To evaluate the comparative efficacy and morbidity of groin radiation therapy in lieu of groin dissection for selected patients with invasive squamous cell carcinoma of the vulva.
- 1.2 To monitor patterns of recurrence and survival of patients treated with groin radiation therapy in lieu of groin dissection.

## 2.0 BACKGROUND AND RATIONALE

Vulvar carcinoma is the fourth most common primary gynecologic cancer, accounting for 3 to 4% of all primary malignancies of the female genital tract. Carcinoma of the vulva occurs predominantly in elderly women, with the highest incidence in the seventh decade. Radical vulvectomy and bilateral groin dissection has, in recent years, become the standard method of therapy (1,2). Radical vulvectomy and inguinal-femoral lymphadenectomy is curative in a high percentage (90-93%) of patients with limited lesions who have no evidence of tumor in resected lymph nodes. (3-6)

Local vulvar tumor control has been excellent with this operation as well. Patients with metastatic tumor in groin lymph nodes have had a significantly poorer outlook, with reported survivals between 24 and 40%. Curry (7) reviewed records of 52 patients at the M.D. Anderson Hospital with positive groin nodes and concluded that patients with 3 or fewer positive nodes have a reasonably good prognosis, but patients with 4 or more positive nodes all succumb to their disease. Much study, therefore, has been directed at risk factors for nodal metastases and correlation with survival.

TABLE I

Node Metastases in Vulvar Carcinoma

	<u>% + Groin Nodes</u>	<u>+ Pelvic Nodes</u>	<u>Overall</u>
Krupp <sup>3</sup>	40/195 = 20.5%	9/40 = 22.5%	(4.6%)
Morley <sup>5</sup>	N <sub>0</sub> =23/120= 19.2% N <sub>1</sub> =7/34 = 20.6% N <sub>2</sub> =53/80 = 66.3%	Not Stated	
Podratz <sup>6</sup>	59/175 = 33.7%	15	(5%)
Curry <sup>7</sup>	57/191 =	9/52 = 17.3%	(4.7%)

GOG Protocol #36, recently completed, has prospectively accumulated surgical pathological data on more than 600 patients who underwent a standardized operative procedure. All these patients were treated during a 6-year interval (11/77 through 2/84), rather than the 19-40 year interval which has been required for single institution studies. Data from this

2.0 BACKGROUND AND RATIONALE (continued)

study is similar to that in the literature. 81.8% of all patients are recurrence-free, and durable local control of the primary lesion has been achieved in 91.9% of all patients. The overall rate of positive groin nodes is 34.3% with increasing risk associated with FIGO stage, grade, depth of invading and maximum diameter of tumor. Groin recurrence has occurred in 2.9% of patients and pelvic recurrence in 1.4%.

TABLE II

Node Metastases in Vulvar Carcinoma  
(GOG #36 & #37)

<u>% + Groin Nodes</u>	
N <sub>0</sub> N <sub>1</sub>	23.7
N <sub>2</sub>	75.3
N <sub>3</sub>	92.6
T <sub>1</sub>	16.4
T <sub>2</sub> , T <sub>3</sub> , T <sub>4</sub>	38.5

Following surgery, however, there has often been a prolonged period of morbidity due to the problems related to wound healing. Lower extremity edema can be progressive and permanent. GOG Protocol #36 has indicated that at least 27% of patients who undergo this operation (all stages) will suffer some degree of chronic lymphedema, and 49% will have some wound breakdown. Podratz (6) observed impairment in primary wound healing in 85% of patients (major and minor) and edema in 69%. Morley (5) reported lymphedema to be "frequent" and wound complications occurred in 50% of patients. Average hospital stay postoperative has been 21.5 days (6). In the GOG series, operative mortality was 1.6%, but mortality in the literature has ranged from 2.2 to 10% (3-6). These complications have predominantly been associated with the groin dissection. Patients who have had vulvectomy without groin dissection have had less frequent complications and shorter hospitalizations (6). These adverse effects are especially bothersome when one notes that 70-80% of all patients in these studies had negative groin nodes. Both Morley (5) and Podratz (6) have observed that clinical staging is confirmed by pathological staging in 75% of cases. While a 25% inaccuracy rate is disconcerting, Podratz's data indicate that, in clinical Stages II and III, pathology downstaged disease more often than upstaged disease (17/31=55%). Hence careful preoperative evaluation of patients should allow the surgeon to identify patients with a reasonably low risk of nodal metastasis.

## 2.0 BACKGROUND AND RATIONALE (continued)

One of the goals in treating patients with carcinoma of the vulva should be to decrease the morbidity of treatment without compromising disease control. The position that surgery is the preferred treatment for the primary lesion in squamous cell carcinoma of the vulva is not challenged. However, adjuvant irradiation may have an important place in allowing a decrease in the radicalism of the surgical procedures used. Elective irradiation of clinically negative lymph node groups has been shown to decrease the subsequent appearance of clinical adenopathy in some disease sites. There is no reason to believe that squamous cell carcinoma of the vulva is inherently different from other squamous cell carcinomas. Large scale studies confirming the effectiveness of radical surgery and radiation therapy have not been performed, but relating the experience of the effectiveness of radiation therapy to control lymph node metastasis in squamous cell carcinoma of the cervix, theoretically this could prove beneficial. GOG Protocol #37 compared pelvic and groin irradiation to pelvic lymphadenectomy for patients who were found to have metastatic disease in the inguinal-femoral nodes at groin dissection. Of the patients who underwent pelvic node dissection, 22.3% had metastases in the pelvic node. This study has shown a significantly superior progression-free interval (70% vs. 51%,  $p=.004$ ) and survival (79% vs. 54%,  $p=.0005$ ) at 2 years for radiation therapy regimen. There was a decrease in groin recurrence from 42.1% to 11.8% in the group which received radiation therapy. Radiation therapy has not been employed as a primary method of therapy because of poor tolerance of vulvar tissue to external beam therapy (1,2). However, there is evidence that radiation therapy is effective in controlling inguinal lymph node metastasis in the disease (8). In this pilot study, six patients were treated with operation to the vulva and groin radiation. One patient with an advanced primary lesion recurred locally. There were no groin recurrences. In a similar, more recent, pilot study at the M.D. Anderson Hospital, 8 additional patients have been treated with good tolerance (9). By substituting groin radiation for groin dissection, a considerable reduction in morbidity could be achieved. No change in local vulvar control would be expected. Radiation therapy has shown that ability to improve PFI and survival in patients with occult vulvar cancer in pelvic nodes, and is expected to control microscopic disease in groin nodes. Patients who undergo the additional risk of operation would have the benefit of the diagnostic information from microscopic examination of the groin nodes. In Frischbier, H.J., Thomsen, K. "Treatment of Cancer of the Vulva with High Energy Electrons" *Am J Obstet Gynec*, 11:431-435, 1971, 118 patients with carcinoma of the vulva received groin irradiation with high energy electrons (10). There was a 70% survival among the patients with NO N1 nodes in this series. No comment was made on the sites of failure or control of the groin, however. There was an 8% overall severe complication rate (all N stages). This may have been related to the large number of N2 and N3 patients treated or to the high dose rate used (300 r/day). In Henderson, R.H., Parsons, J.T., Morgan, L., Million, R.R., "Elective Ilio-inguinal Lymph Node Irradiation" *Int J Rad Onc Biol Phys*, 10:811-819, 1984, 91 patients all with NO and N1 groin nodes were treated with groin radiation (11). Most of these patients

2.0 BACKGROUND AND RATIONALE (continued)

had vulvar cancer, but several had cervical, vaginal and penile cancers as well. There were no failures in the radiation field in the groin, but two of forty-nine patients failed in the groin outside of the treatment field. There was one severe complication, hip fracture, in a patient treated with cobalt. These two studies taken with the extensive data in treatment of head and neck patients would help justify a large scale Phase III trial in vulvar cancer.

We propose a randomized comparison of radiation therapy to the groin versus groin node (inguinal-femoral) dissection (each combined with standard surgical therapy to the primary lesion) in selected patients with invasive squamous carcinoma of the vulva.

### 3.0 PATIENT ELIGIBILITY

#### 3.1 Eligible Patients

3.11 Patients with primary, previously untreated, histologically confirmed invasive squamous cell carcinoma of the vulva clinically determined to be Stage I through III (see Appendix III for staging criteria) that radical vulvectomy would suffice to remove all of the primary lesion. The eligible substages include:

$T_1N_0M_0$  if the patient is not eligible for GOG Protocol #74

$T_1N_1M_0$  (vascular involvement or invasion greater than 5 mm)

$T_2N_0M_0$

$T_2N_1M_0$

$T_3N_0M_0$

$T_3N_1M_0$

3.12 Patients whose histological cell type is invasive squamous cell carcinoma of the vulva.

3.13 Patients who have signed an informed consent for the study.

3.14 Patients who have met the pre-entry requirements specified in Section 7.0.

#### 3.2 Ineligible Patients

3.21 Patients with other than primary squamous cell carcinoma of the vulva, or lesions less than invasive. Histologic variants of squamous cell carcinoma, such as baso-squamous carcinoma, basal cell carcinoma, verrucous carcinoma, mullerian carcinoma, squamous carcinoma in condyloma acuminatum, pseudoglandular squamous cell carcinoma, cloacogenic carcinoma and Bowen's disease with squamous carcinoma.

3.22 Patients with  $T_1N_0M_0$  or  $T_1N_1M_0$  who meet the eligibility criteria for GOG Protocol #74. Patients with T4 lesions, N2 or N3 groin nodes and patients with distant metastasis (M1). Patients with cytologically positive groin nodes.

3.23 Patients with recurrent invasive carcinoma of the vulva, irrespective of the type of previous treatment.

3.24 Patients who, for any reason, have been previously treated with irradiation or chemotherapy.

3.25 Patients with hemapoietic depression at the onset of the study: white count less than 3,000 or platelet count less than 100,000.

- 3.26 Patients with septicemia or severe infection.
- 3.27 Patients with severe gastrointestinal symptoms and/or gastrointestinal bleeding.
- 3.28 Patients with signs of renal impairment: creatinine greater than 2.0.
- 3.29 Patients with circumstances that will not permit completion of the study or the required follow-up.
- 3.30 Patients with prior or concomitant malignancy except skin (excluding melanoma).
- 3.31 Patients not operable for medical or other reasons.
- 3.32 Patients with GOG Performance Grade of 4.

#### 4.0 STUDY MODALITIES

Patients with invasive squamous cell carcinoma of the vulva who meet eligibility criteria will be randomized between radical vulvectomy and groin dissection and radical vulvectomy and groin radiation therapy. Complete clinical and radiographic evaluation should be performed prior to randomization (see Section 7.0). Needle aspiration cytology must be performed if there is any concern over groin node status. PATIENTS WITH SUSPICIOUS ENLARGED GROIN NODES ARE NOT ELIGIBLE FOR THIS STUDY.

#### 4.1 Surgical Procedure

##### 4.11 Radical Vulvectomy and Groin Node Dissection (Appendix IV) (Treatment Regimen I: see Section 5.21)

All patients will undergo surgery as described in Appendix IV (Vulvar Procedures). At the option of the surgeon, the radical vulvectomy can be performed before or after the bilateral groin node dissection.

##### 4.12 Radical Vulvectomy (Appendix IV) (Treatment Regimen II: See Section 5.22)

All patients will undergo surgery as described in Appendix IV (Vulvar Procedures).

##### 4.13 Modified Radical Hemivulvectomy (Appendix V) (STAGE I PATIENTS ONLY)

Those patients with Stage I disease (T1N0M0, T1N1M0) who are eligible for this protocol (See Section 3.0) may, at the discretion of the treating physician, undergo a modified radical hemivulvectomy in lieu of radical vulvectomy if the modified operation can encompass the primary disease with adequate margins.

#### 4.2 Radiation Therapy

##### 4.21 Radical Vulvectomy and Bilateral Groin Radiation (Treatment Regimen II: see Section 5.22)

4.211 All patients randomized to receive radiation therapy should have therapy instituted no more than four weeks postoperatively. Radiotherapists should see all patients prior to randomization or surgery.

4.212 Dose Distribution

- 4.2121 The dose to each inguinal area will be 5000 cGy given over 5-6 weeks calculated at a depth of 3 cm from the anterior skin surface. It is recommended that 50% of this dose be given with electron beam of approximately 12-13 MeV in order to reduce the dose to the underlying femoral heads.
- 4.2122 Photon therapy must be given with at least 4-6 MeV x-rays of 60 Co gamma rays with a treatment distance of 80 cm or greater. Use of an electron beam for part of the groin treatment is recommended.
- 4.2123 Treatment will be given in the supine position five days a week. Patients with a fatty abdominal apron will have this retracted to minimize self-bolusing skin folds.

4.213 Fields

Bilateral groin irradiation: Two separate anterior hexagonal fields will be used. (See Appendix VI).

- 4.2131 The superior border will be at the level of the anterior superior iliac spine.
- 4.2132 The superomedial border will be 2 cm above a line drawn from the anterior superior iliac spine to the pubic tubercle.
- 4.2133 The medial borders will be perpendicular 2 cm from the midline. Medial border should extend no further lateral than medial border to obturator foramina.
- 4.2134 The lateral border will drop vertically from the anterior superior iliac spine.
- 4.2135 The inferolateral border will be parallel to 8 cm below the line joining the anterior superior iliac spine and the pubic tubercle.
- 4.2136 The inferior border will be at a level below the most inferior part of the vulva.
- 4.2137 The pelvic (iliac) node bearing areas are NOT to be treated and no boost will be given to the primary site.

#### 4.22 Postoperative Therapy for Positive Groin Nodes

4.221 All patients on Regimen I (groin dissection) who have metastatic carcinoma in resected nodes will receive radiation therapy to the ipsilateral groin and hemi-pelvis.

The GOG Operations Office must be notified by phone prior to entry of the patient onto radiation therapy. Radiation therapy should be instituted no more than four weeks post-operatively, at the time of adequate healing. If possible, radiotherapists should see patients prior to randomization or surgery.

#### 4.222 Dose Distribution

4.2221 Patients are to receive 5000 cGy in 25 fractions over 5 weeks to the midplane of the pelvis, halfway between the superior border of the obturator foramen and L5-S1 interspace. The same dose is to be delivered to the center of the inguinal and femoral node areas at a depth of 3 cm from the anterior surface. Anterior and posterior fields will be used to treat the pelvic nodes, and these will both be treated on each treatment day, with equal loading. The part of the anterior field covering the inguinal-femoral nodes, which is not opposed by the posterior field will be boosted, preferably with 12-13 MeV electrons to bring the tumor dose to 4500-5000 cGy at 3 cm. The dose to the boost field will be given in increments of 125 cGy TD/fraction spread equally over the time of treatment. In the event that extracapsular nodal disease is present in the dissected inguinal nodes, the boost dose will be increased by 500 cGy.

4.2222 Photon therapy must be given with at least 4-6 MeV x-rays or 60 Co gamma rays with a treatment distance of 80 cm or greater. Use of an electron beam for part of the groin treatment is recommended.

4.2223 Treatment will be given in the supine position. Patients with a fatty abdominal apron will have this retracted to minimize self-bolusing skin folds.

4.223 Fields

Pelvic and Groin Irradiation: Two separate fields will be used.

Anterior Field (Appendix VI b)

4.2231 The superior border of the pelvic field will be the mid sacroiliac joint.

4.2232 The medial border will be perpendicular 2 cm from the midline. Medial border should extend no further lateral than medial border of the obturator foramen.

4.2233 The superolateral corner will be at the anterior superior iliac spine. The superolateral border is to be shaped in order to shield the maximum amount of ileum.

4.2234 The lateral border will drop vertically from the anterior superior iliac spine.

4.2235 The inferolateral border will be parallel to and 8 cm below the line joining the anterior superior iliac spine and the pubic tubercle.

4.2236 The inferior border will be at a level below the most inferior part of the vulva.

Posterior Field (Appendix VI c)

4.2237 The superior and medial borders will coincide with the anterior fields.

4.2238 The lateral border will be 1 cm lateral to the widest part of the true pelvis.

4.2239 The inferior border will be at the level of the superior border of the obturator foramen.

Anterior Boost Field (Appendix VI b)

4.2240 This will cover the area of the anterior field not opposed by the posterior field. NB In defining boost field, appropriate allowance must be made for the divergence of the posterior field's exit dose.

4.23 Dose Modification

4.231 CBC and platelet counts are to be obtained at least at weekly intervals.

If WBC is less than 1500, radiotherapy is to be suspended until WBC is 2000 or over.

If hemoglobin is less than 10.0 grams or PCV is less than 30%, radiotherapy is to be suspended until patient is transfused and hemoglobin is 11.0 grams or over or PCV is 33% or greater.

If platelet count is less than 60,000, radiotherapy is to be suspended until platelet count is 80,000 or greater.

4.232 Every effort should be made to adhere to the dose fractionation regimen prescribed. In the event that moist skin desquamation occurs, an interruption in treatment will be permitted so long as the overall duration of treatment is not increased by more than one week.

4.24 Reports (See Section 10.0)

4.241 Radiation therapy reporting sheets are to be completed and forwarded to the Operations Office at the conclusion of treatment.

4.242 Copies of the portal films and a Polaroid photograph of the patient in treatment position with portals outlined on the skin are to be forwarded to the Operations Office by completion of first week of therapy.

4.25 Rapid Film Review

The American College of Radiology will review pretreatment films, calculations, and plan of treatment. The following information will be needed for this review within 1 week after radiation therapy begins:

- One copy each of simulator and verification films
- Initial calculations
- Representative film of initial field

4.26 Radiation Therapy Quality Control and Documentation

The Radiologic Physics Center, under the sponsorship of the American Association of Physicists on Medicine, will supervise the dosimetry control for this clinical trial. To participate in the trial, the institution 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.

4.3 Pathology Material and Slides

The GOG Pathology Committee has determined that meticulous handling and reporting of the vulvar specimen is extremely important for pathologic evaluation and clinicopathologic determinations. The recommended guidelines for handling of the specimens are as follows:

A. Anatomic Location (should be described in detail)

1. Labium majus (right or left)
  - upper third
  - middle third
  - lower third
2. Labium minus -- same as labium majus
3. Clitoris
4. Perineum

B. Size of lesion

Greatest surface dimensions: \_\_\_\_\_ cm x \_\_\_\_\_ cm  
 Deepest penetration of tumor: \_\_\_\_\_ mm

C. Lymph Nodes

Size of nodes \_\_\_\_\_  
 Type of involvement: \_\_\_\_\_ Gross \_\_\_\_\_ Microscopic

Nodes larger than 4 mm may be quartered rather than bisected to increase the possibility of detecting the foci of microscopic tumor. See Diagram in Appendix VII as guideline for node evaluation.

D. Microscopic Grading

The microscopic grading of the tumor will be in accord with guidelines of the Pathology Committee.

E. Required Specimens for Quality Control Procedure

1. Stained slides demonstrating the deepest penetration of the tumor.
2. Stained slides of positive lymph nodes. The nodes should be properly labeled as to location during operation by the surgeon because the pathologist cannot determine the location once the specimen has been resected.

ALL INFORMATION MUST BE RECORDED ON FORM F.

## 5.0 PATIENT ENTRY/RANDOMIZATION AND TREATMENT PLAN

An original, signed form HHS-596, indicating prior approval by the institution's Human Rights or Clinical Trials Committee for participation in this study must be forwarded to the GOG Operations Office before patient entries onto the study will be accepted. In addition, a copy of the informed consent being used (if it differs from the suggested form appended to the protocol) or a letter from the Principal Investigator stating that the suggested form is being used, must accompany the HHS-596.

### 5.1 Telephone Entry

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

- 5.11 A Consent Form must be signed by the patient or guardian.
- 5.12 Make certain all eligibility requirements according to Section 3.0 have been met.
- 5.13 Fast Fact Sheet data should be gathered. With this data in hand, the GOG Operations Office in Philadelphia should be called via the "WATS" line: 1-800-523-2917 (in Pennsylvania, where applicable, call 1-215-854-0722) Monday through Friday, 9 am to 5 pm EST/EDT.
- 5.14 Randomization will take place on the telephone after consideration of Fast Fact Sheet data.
- 5.15 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

### 5.2 Treatment Plan

- 5.21 Regimen I: Radical vulvectomy and groin node dissection (see Section 4.1 and Appendix IV).
- 5.22 Regimen II: Radical vulvectomy and groin irradiation.
  - 5.221 Radical vulvectomy will be performed in the standard fashion (see Section 4.1 and Appendix IV).
  - 5.222 Radiation therapy should be started no later than four weeks following the date of surgery (see Section 4.21 for details of radiotherapy treatment.) All patients will receive bilateral groin radiation therapy.

### 5.23 Positive Groin Nodes

Patients on Regimen I who have metastatic carcinoma in resected nodes will receive radiation therapy to the ipsilateral groin and hemi-pelvis (see Section 4.22).

6.0 TREATMENT MODIFICATIONS

6.1 Surgery

Those patients with Stage I disease (T1N0M0, T1N1M0) who are eligible for this protocol (see Section 3.0) may, at the discretion of the treating physician, undergo a modified radical hemivulvectomy (Appendix V) in lieu of radical vulvectomy if the modified operation can encompass the primary disease with adequate margins.

6.2 Radiation Therapy

Should excessive myelosuppression or desquamation occur, radiotherapy can be delayed up to one week.