

RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-12

PHASE II STUDY OF CHEMORADIATION IN PATIENTS WITH LOCALLY EXTENSIVE EPIDERMOID CARCINOMA OF THE VULVA

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WITH LOCALLY EXTENSIVE EPIDERMOID CARCINOMA OF THE VULVA.**

SCHEMA (see reverse for Group B, Node +)

Eligible Patients: Patients with locally extensive epidermoid cancers of the vulva involving or approaching midline structures who are not candidates for radical vulvectomy (*non-exenterative surgery*) as initial therapy because of anticipated compromise of bowel or bladder continence, or impairment of sexual function. Age \geq 18, KPS 60 or greater, no prior invasive malignancy for 5 yrs., no prior pelvic or perineal radiotherapy, no prior chemotherapy within 48 months. Pregnant patients ineligible. Absolute neutrophil count \geq 1800/mm³, platelets \geq 150,000/mm³. **Required Sample Size: 99**

GROUP A - PATIENTS WITH CLINICALLY NEGATIVE GROIN NODES:(OPTION 1)

Patients must have groin nodes free of metastatic contamination by clinical and diagnostic imaging criteria which may include biopsy.

TREATMENT (Step 1 registration)

45.0 Gy/25 FX/5 weeks administered to the primary cancer, inguino-femoral nodes, and low pelvic external iliac nodes.

PLUS:

2 courses of concurrent (*synchronous*) chemotherapy during the first and fifth weeks of radiation, each to consist of: 5FU 1000 mg/m²/24 hrs. X 96 hrs by continuous IV infusion during fractions 2,3,4,5 and 22,23,24,25 of radiotherapy. Mitomycin-C 10mg/m² IV bolus with RT fractions 2 and 22 (*weeks 1 and 5 of radiotherapy*)

**JOINT RE-EVALUATION BY SURGEON AND RADIATION ONCOLOGIST
12-14 DAYS AFTER COMPLETION OF SECOND COURSE OF CHEMORADIATION:**

**ASSESSMENT OF RESPONSE AT THE PRIMARY SITE FOLLOWED BY
RE-REGISTRATION (Step 2) WITH RTOG HEADQUARTERS TO:**

<u>OPTION 3</u>	OR	<u>OPTION 5</u>	OR	<u>OPTION 7</u>
COMPLETE CLINICAL RESPONSE		PARTIAL RESPONSE RESECTABLE*		PERSISTENT DISEASE UNRESECTABLE*
5FU 1000 mg/m ² / 24 hrs x 96 hrs during fractions 27,28,29,30 of "Consolidative" daily radiation. 9.0 Gy/5 Fxs (54.0 Gy total to primary)		conservative local excision* sparing midline structures. 3-6 weeks after chemoradiation		5FU 1000 mg/m ² / 24 hrsx 96 hrs during fractions 28-35 of "Boost" BID radiation. 18.0 Gy/10 Fxs 5 days. MIT-C 10 mg/m ² with fraction 28. (63.0 Gy total to primary)

SALVAGE SURGERY PERMITTED AT 6 WEEKS FOR PERSISTENT CANCER

* Denotes response sufficient to permit conservative surgical removal of persistent palpable and visible disease without anticipated functional compromise of normal midline structures. (*bladder, ano-rectum, or clitoris and vagina in patients desiring to remain sexually active.*)

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GROUP B - PATIENTS WITH POSITIVE GROIN NODES: (OPTION 2)

Patients must have undissected groin nodes with biopsy proven metastatic contamination prior to registration.

TREATMENT (Step 1 Registration)

Bilateral superficial groin dissections. Deep groin dissection(s) if required to remove all nodes larger than 1.0 cm. (*Intraoperative Lymphatic Mapping is optional*)

TO BE FOLLOWED WITHIN 21 DAYS OF SURGERY BY:

45.0 Gy/25 FX/5 weeks administered to the primary cancer, and low pelvic external iliac nodes.
50.4 Gy/28 FX/5.6 weeks to the inguino-femoral nodes.

PLUS:

2 courses of concurrent (*synchronous*) chemotherapy during the first and fifth weeks of radiation, each to consist of:
5FU 1000 mg/m²/24 hrs. X 96 hrs by continuous IV infusion during fractions 2,3,4,5 and 22,23,24,25 of radiotherapy.
Mitomycin-C 10mg/m² IV bolus with RT fractions 2 and 22 (*weeks 1 and 5 of radiotherapy*)

**ASSESSMENT OF RESPONSE AT THE PRIMARY SITE FOLLOWED BY
RE-REGISTRATION (Step 2) WITH RTOG HEADQUARTERS TO:**

<u>OPTION 4</u>	OR	<u>OPTION 6</u>	OR	<u>OPTION 8</u>
COMPLETE CLINICAL RESPONSE		PARTIAL RESPONSE RESECTABLE*		PERSISTENT DISEASE UNRESECTABLE*
5FU 1000 mg/m ² / 24 hrs x 96 hrs during fractions 30,31,32,33 of "Consolidative" daily radiation. 9.0 Gy/5 Fxs (54.0 Gy total to primary)		conservative local excision* sparing midline structures. 3-6 weeks after chemoradiation		5FU 1000 mg/m ² / 24 hrs x 96 hrs during fractions 31-38 of "Boost" BID radiation. 18.0 Gy/10 Fxs 5 days. MIT-C 10 mg/m ² with fraction <u>31</u> . (63.0 Gy total to primary)

SALVAGE SURGERY PERMITTED AT 6 WEEKS FOR PERSISTENT CANCER

* Denotes response sufficient to permit conservative surgical removal of persistent palpable and visible disease without anticipated functional compromise of normal midline structures. (*bladder, ano-rectum, or clitoris and vagina in patients desiring to remain sexually active.*)

Institution # _____

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ELIGIBILITY CHECK (STEP 1)

Case # _____

(page 1 of 2)

- _____(Y) 1. Does the patient have a histopathologic diagnosis of primary epidermoid/squamous carcinoma of the vulva?
- _____(Y) 2. Was the patient formally evaluated by a gynecologic oncologist?
- _____(N) 3. Is the patient a candidate for initial therapy by radical vulvectomy?
- _____(≥ 1800) 4. What is the ANC?
- _____(≥ 150) 5. What are the platelets (*x 1000*)?
- _____(Y) 6. Is the hematocrit > 30%?
- _____(N) 7. Does the patient have chronic blood dyscrasias, leukemia or HIV infection?
- _____(N) 8. Is there any suspicion of distant or pelvic node metastasis as assessed by one of the methods in Section 3.1.6?
- _____(Y/N) 9. Were any inguino-femoral nodes > 1.0 cm detected by palpation or radiographic means?
(If no, skip to Q12)
- _____(Y/N) 10. Was each involved side excisionally biopsied and found negative for mets?
(If yes, skip to Q12)
- _____(Y) 11. Will the patient undergo superficial groin node dissection?
- _____(N) 12. Has the patient had an invasive malignancy within the last 5 years?
- _____(N) 13. Any cytotoxic chemotherapy within the last 48 months?
- _____(N) 14. Any prior pelvic or perineal radiotherapy?
- _____(N) 15. Is the patient pregnant?
- _____(Y) 16. Does the patient have a KPS of ≥ 60 and a life expectancy of at least 3 years?
- _____(≥ 18) 17. What is the patient's age?

(continued on next page)

Institution # _____

RTOG 96-12

ELIGIBILITY CHECK (STEP 1)

Case # _____

(page 2 of 2)

_____(Y) 18. Has the patient signed a study-specific informed consent?

Patient's Name

Verifying Physician

Patient ID #

Referring Institution # (if different)

Medical Oncologist

Birthdate

Sex

Race

Social Security Number

Zip Code (9 digit if available)

Method of Payment

Treatment Start Date (must be after registration)

Treatment Assignment

Completed by _____

Date _____

Institution # _____

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ELIGIBILITY CHECK (STEP 2)

Case # _____

_____(Y/N) 1. Will the patient continue on to further protocol treatment? (*If no, call to HQ must still be made*)

_____(A/B) 2. What was the patient's initial group?

_____ 3. What was the result of the re-evaluation?
(*complete response; partial response, resectable; persistent disease, unresectable*)

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # (*if different*)

_____ Treatment Start Date for the Second Phase of Treatment

_____ Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

In the past two decades, the medical management of patients with invasive squamous carcinoma of the vulva has undergone radical reappraisal. Corresponding to trends in the management of malignancies at other primary sites, increasing attention has been focused on strategies to conserve structure and function of critical normal tissues without compromising cancer control or survival. Boronow^{1,2} pioneered the integrated use of moderate dose preoperative or postoperative radiation with conservative surgery as an alternative to exenterative surgery. His favorable experiences were subsequently replicated and confirmed by other investigators who additionally observed that modest dose preoperative radiation could result in complete histologic tumor clearance in the operative specimens of approximately 50% of patients with locally advanced vulvar cancer.^{3,4,5}

Successes in the conservative management of squamous cancers of the anal canal achieved through the synchronous administration of radiation and cytotoxic chemotherapy^{6,7,8} (*Chemoradiation*) predictably stimulated interest in applying this approach to patients with locally advanced squamous cancers of the vulva. Reports from single institutions have been very promising, including favorable experience with chemoradiation without surgery in medically inoperable or technically unresectable patients, as well as patients with loco-regional recurrence following radical surgery.⁹⁻¹⁸ Experience with a limited number of patients suggests that chemoradiation may provide equivalent or better loco-regional cancer control than would be expected from exenterative surgery,¹⁹ with functional sequelae more acceptable to the patients. Frequently, preoperative chemoradiation succeeds in converting tumors from extensive cancers (*which would require partial or total exenteration if managed by initial radical surgery*) to limited lesions amenable to conservative local excision of reduced residual volume.⁹⁻¹⁸

5-Fluorouracil (*5-FU*) has been employed as an enhancer of local radiation response in virtually all reports of chemoradiation treatment of vulvar cancer in North America. Mitomycin-C (*Mit-C*) and Cisplatin have been used as second agents in conjunction with 5-FU, although some patients have been treated with 5-FU as the sole radioenhancer. Based on the outcome of the randomized intergroup anal canal study (*RTOG 87-04/ECOG 1289*) which compared 5-FU with radiation to 5-FU + Mit-C with radiation and revealed a local control advantage to the addition of Mit-C to 5-FU, this protocol will employ 5-FU and Mit-C for two courses during the first and fifth weeks of radiation. Selected patients whose response is inadequate to permit conservative surgical excision may receive Mit-C along with 5-FU in concert with a "boost" course of radiation to a reduced volume.

Radical inguino-femoral node dissection has been part of the standard therapy of patients with locally extensive vulvar cancer for almost fifty years.^{20,21} The groin nodes represent the first echelon of lymphatic spread from vulvar neoplasia,^{22,23} and even when palpably non-suspicious will be microscopically contaminated in approximately 20% of patients subjected to therapeutic node dissection.²⁴⁻²⁹ Acute complications of radical lymphadenectomy include infection, wound dehiscence, thrombophlebitis, venous thrombosis, and pulmonary embolism. Delayed sequelae include lymphedema of the lower extremities, which may be transient or permanent.

Elective or prophylactic irradiation of regional lymph nodes has long been successfully employed in the treatment of malignancies at a variety of anatomic sites where lymph nodes are either inaccessible to complete surgical removal, or where therapeutic node dissection is functionally or cosmetically debilitating. Elective groin irradiation has been advocated as a therapeutic alternative to inguino-femoral lymphadenectomy when the groins are palpably uncontaminated,³⁰ but most published series report a small, but distressing incidence of groin recurrence in such patients.³⁰⁻³⁴ Recurrence in the groin is usually lethal.³⁴⁻³⁹ Salvage therapy is rarely efficacious, regardless of the modalities employed.

The Gynecologic Oncology Group conducted a prospective randomized trial comparing groin irradiation to therapeutic groin dissection in selected patients with vulvar cancer. That study was terminated early due to an unacceptable rate of groin node failures (*5/27 patients, 18.5%*) observed in the group assigned to radiation, all of whom subsequently died of their disease.³⁴ Technical inadequacies in radiation administration may have inadvertently caused substantial underdosage of inguino-femoral nodes resulting in the observed failures and serving to emphasize the importance of technique, treatment planning, and proper dosimetry in contriving a treatment strategy based all, or in part, on radiation.^{40,41} Groin failure may have been the consequence of technically inadequate dose distribution caused by the intention to limit dose administered to the femoral necks.

Since then, two reports, on a total of 36 patients, have described the results of elective chemoradiation to the groins in patients undergoing preoperative or definitive chemoradiation for locally extensive vulvar primaries. With median follow-up exceeding 30 months in both studies, no patient has relapsed within the irradiated groins.^{42,43}

This protocol will attempt to replicate, in the cooperative group setting, the favorable results reported from Sacramento⁴² and Loma Linda.⁴³

A prospective, randomized trial conducted by the GOG compared pelvic lymphadenectomy with irradiation of the groins and pelvic nodes as additional therapy for patients found to have contamination of inguino-femoral nodes at the time of radical vulvectomy and superficial and deep groin dissection. Relapse free survival was statistically superior in the group of patients randomized to radiation.⁴⁴

Based upon this study, adjuvant radiation has become widely accepted as the standard of care in patients with involvement of two or more groin nodes. Unfortunately, permanent, often disabling, lower extremity lymphedema is the common sequel of radiation superimposed on radical superficial and deep inguino-femoral lymphadenectomy. Limiting the scope of groin dissection prior to groin chemoradiation may be an avenue to reduce both acute perioperative complications as well as chronic iatrogenic lymphedema. In this protocol, patients presenting with clinically apparent, histologically confirmed metastasis to one or more groin nodes will initiate treatment with bilateral groin dissections of sufficient scope to remove all nodes superficial to the cribriform fascia as well as all nodes palpably or radiographically larger than 1.0 cm which may lie below the cribriform fascia. Radical deep groin dissection and pelvic lymphadenectomy will not be done. Intraoperative lymphatic mapping with Isosulfan Blue may be done as an optional study in some patients undergoing limited groin dissections, but will not be a required study. Limited groin dissections will be followed by chemoradiation directed to the primary, bilateral groins, and pelvic nodes, with subsequent treatment of the primary tumor to be contingent upon response.

Treatment of the primary tumor will be identical for both patients with clinically negative groin nodes as well as patients with positive nodes. Patients achieving a complete clinical response to modest dose chemoradiation will undergo limited, consolidative chemoradiation directed to the primary site. Patients who experience a partial response sufficient to permit local removal of residual disease without functional compromise of midline structures will undergo conservative surgery 3-6 weeks after chemoradiation. Patients whose response is insufficient to allow conservative surgery will have a third course of 5-FU and Mit-C in concert with twice daily, accelerated "Boost" radiation delivered to a reduced volume. Exenterative surgery will not be employed except as a final resort for patients with biopsy confirmed residual disease six weeks after completion of chemoradiation. When feasible, less extensive surgery will be allowed and encouraged should additional tumor shrinkage have rendered this feasible. Further surgery to the treated inguino-femoral or pelvic nodal areas will not be undertaken except for biopsy proven disease recurrence.

2.0 OBJECTIVES

- 2.1** To assess the efficacy of chemoradiation targeted to the inguino-femoral nodes as an alternative to groin dissection in patients with clinically uncontaminated groin nodes who will be undergoing preoperative or definitive chemoradiation for locally extensive epidermoid cancer of the vulva. To confirm, in the context of a larger, multi-institutional investigation, the favorable results of such therapy reported in a limited number of patients from single institution studies.
- 2.2** To assess the efficacy of limited groin dissection and chemoradiation as a potentially less chronically morbid alternative to superficial and deep groin dissection followed by radiation directed to the groins and pelvis (*conventional therapy*) for patients with clinically apparent groin node metastasis at the time of diagnosis.
- 2.3** To measure the efficiency of initial chemoradiation in converting the status of locally advanced cancers of the vulva from **unresectable** except by exenterative surgery, to **resectable** by surgery conserving functional midline structures.
- 2.4** To assess and quantitate the acute morbidities and late effects in normal tissues consequent to such treatment.
- 2.6** To quantitate the following endpoints:
 - 2.6.1** Freedom from relapse in groin nodes in a population of patients undergoing elective chemoradiation to the groins without surgical dissection.
 - 2.6.2** Freedom from relapse in the groins in a population of patients with histologically confirmed inguino-femoral node metastasis treated by limited surgical removal of all palpably enlarged nodes followed by regional chemoradiation.
 - 2.6.3** Rate of chemoradiotherapeutic conversion of locally extensive vulvar cancer from unresectable to resectable using conservative surgery preserving the function of critical midline structures.
 - 2.6.4** Freedom from relapse at the primary site in patients managed with chemoradiation alone and patients

managed with preoperative chemoradiation and local excision.

2.6.5 Acute toxicities of treatment and late effects in normal tissues (*LENT*).

2.6.6 Pattern of failure and causes of death.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Patients must have a histopathologic diagnosis of primary epidermoid/squamous carcinoma of the vulva. Patients may have primary cancers of the Bartholin's gland or duct provided that the histology is squamous.

3.1.1.1 Verrucous carcinoma, melanoma, adenocarcinoma, adenoidcystic carcinoma, and all other histologic types are excluded.

3.1.2 Patients must be formally evaluated by a gynecologic oncologist prior to study entry. The specific anatomic limitation on initial conservative surgery must be specified by the gynecologic oncologist at the time of study registration.

3.1.3 Based on the extent of the primary lesion, patients must not be candidates for initial therapy by radical vulvectomy. This will usually entail cancer extension to, or invasion of, a midline structure such as anus, rectum, urethra, or bladder. Additional criteria include an anticipated surgical margin of less than 1.0 cm grossly⁴⁵ (*8 mm in fixed tissue*), adherence to or invasion of bone, or proximity to, or invasion of, the clitoris or vagina in patients desiring potential conservation of sexual function. A clinical margin of 1.0 cm of grossly uninvolved tissue is intended to serve only as a guideline, recognizing that there may be circumstances (*particularly with very large tumors and cancers with infiltrative growth patterns*) in which a larger margin is deemed desirable by the gynecologic oncologist, but not achievable without functional compromise of midline anatomic structures.

3.1.4 Absolute neutrophil count must be $\geq 1800/\text{mm}^3$, and pre-treatment platelets must be $\geq 150,000/\text{mm}^3$. Hematocrit must exceed 30% or be brought to this level through the use of erythropoietin or transfusion. Patients with chronic blood dyscrasias or leukemia are not eligible for this study.

3.1.5 Patients known to be HIV infected are ineligible because of their increased vulnerability to the predictable acute toxicities of protocol therapy. Patients are not required to be tested for the presence of HIV, but testing is strongly recommended for patients with a history which has rendered them at risk for acquisition of the infection.

3.1.6 There can be no suspicion of remote metastasis or pelvic node metastasis (*M1 disease*) based on the mandatory pre-registration PA and lateral chest x-ray and abdomino-pelvic CT scan or MRI.

3.1.7 In patients to be treated with elective chemoradiation to the groins, palpation of the inguinal areas must be negative for gross metastatic disease. If inguino-femoral nodes larger than 1.0 cm are appreciated, either by palpation or by CT or MRI, at least one such node (*or two in the eventuality that both groins are problematical*) must be excisionally biopsied and found to be negative for metastasis prior to study registration.

3.1.8 For patients to be treated with superficial groin dissection prior to chemoradiation, histologic confirmation of node metastasis must be obtained by fine needle aspiration or excisional biopsy prior to patient registration. Involved groin nodes must be considered resectable in the judgement of the attending gynecologic oncologist. Patients with matted, fixed, or ulcerated nodes are unlikely to be suitable for this study.

3.1.9 Patients may not have had another invasive malignancy during the 5 years prior to study entry. Patients with a history of cervical, vaginal, or vulvar intra-epithelial neoplasia (*CIN, VAIN, or VIN*), basal cell epitheliomas of the skin, or intraductal carcinoma of the breast may be entered on study.

3.1.10 Patients with a past history of malignancy may not have received cytotoxic chemotherapy within 48 months. Patients with a remote history of carcinoma of the breast may have received Tamoxifen within 48 months, or may be under treatment with Tamoxifen.

3.1.11 Patients may not have undergone prior pelvic or perineal radiotherapy.

3.1.12 Patients who are pregnant will not be registered on this protocol. Patients who may possibly be pregnant will undergo pregnancy testing prior to study entry.

3.1.13 Karnofsky Performance Score of $60 \geq$ (*Appendix II*) and a life expectancy of at least 3 years.

3.1.14 Patients must be ≥ 18 years of age.

3.1.15 Patients must sign a study-specific informed consent form. (*Appendix I*).

4.0 PRE-TREATMENT EVALUATION

4.1 A history must be recorded concerning the baseline function of structures and anatomic organs to be included within the irradiated volume. Specifically, the patients baseline bowel and bladder function shall

be recorded, as well as whether there is a history of symptomatic diverticular disease, inflammatory bowel disease, or prior pelvic surgery. The patient's hormonal status shall be ascertained and, if applicable, her age at menopause and whether or not hormonal replacement therapy (*HRT*) has been employed. A reproductive history should be obtained. Any history of osteoporosis or of bone fracture should be noted. Symptoms of peripheral vascular disease or of peripheral neuropathy should be stated, and any history of leg edema recorded. The patient's baseline sexual function should be specified.

- 4.2** Meticulous description of the anatomic extent of the primary lesion and assignment of T stage using the FIGO/AJCC staging classification of 1988 (*Appendix III*). Palpatory findings in the inguinal areas are to be scrupulously recorded. Clinical color photographs or slides of the primary lesion are required both to document initial distribution of disease as well as to aid in planning potential reduced volume consolidative therapy or reduced volume "boost" therapy. Clinical photographs will be repeated annually in follow-up for the documentation of late skin effects.
- 4.3** The general physical exam should comment on whether or not femoral, dorsalis pedis, and posterior tibial arterial pulses are detectable, whether or not bruits can be discerned in the groins and whether there are venous varicosities present or leg edema. In addition to describing the extent and growth pattern of the primary tumor, the pelvic examination should record the presence of vulvar dystrophies, the presence of atrophic vaginitis, the presence of cystocele or rectocele, the presence of hemorrhoids, and the strength and competence of the anal sphincter. The examination should include inspection of the cervix and full vaginal barrel, as well as digital palpation of the distal rectum and anus to exclude coexistent neoplasia.
- 4.4** Pre-treatment height and weight must be recorded.
- 4.5** Complete blood counts and differential. Chemistry panel to include serum electrolytes, BUN and creatinine, total protein, albumin, calcium, phosphate, and liver enzymes.
- 4.6** PA and lateral chest radiographs.
- 4.7** CT scan of the abdomen and pelvis. Enteric and intravenous contrast are strongly advised unless medically contraindicated. The CT scan must extend caudally to assess the entire inguino-femoral node chains both to look for enlarged nodes, as well as to assist in dosimetric planning (*see Section 6.0*). MRI of the abdomen, pelvis, and inguinal areas may be substituted for CT at the discretion of the radiation oncologist.
- 4.8** Nodal Evaluation
- 4.8.1** Negative excisional biopsy of at least 1 node from each groin harboring nodes which are larger than 1.0 cm by palpation or by CT or MR imaging for patients who are to be registered to the node negative treatment assignment.
- 4.8.2** Patients for whom such a biopsy reveals metastatic spread to a groin node become eligible for protocol therapy according to the node positive treatment assignment.

5.0 REGISTRATION PROCEDURES

5.1 First Registration

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information (*Group A [node (-) vs. Group B [node +]*)
- Demographic Data
- Treatment Start Date (*must be after registration*)

5.2 Second Registration:

Patients must be re-registered to the second phase of treatment within 2 weeks following completion of the initial treatment phase by calling the RTOG registrar (215/574-3191). A second registration call is required regardless of the response to treatment or the inability to continue with a second phase of treatment. Failure to call in the second registration will result in data delinquencies. Based upon the initial response to treatment and resectability status, additional treatment will be assigned as follows:

- 5.2.1** Group A Patients (negative groin nodes) will be assigned one of the following options:
- Option 3 - Consolidation chemoradiation for complete clinical response
 - Option 5 - Conservative local excision for resectable partial response

- Option 7 - Additional chemoradiation for unresectable persistent disease
- 5.2.2** Group B Patients (positive groin nodes) will be assigned to one of the following options:
 Option 4 - Consolidation chemoradiation for complete clinical response
 Option 6 - Conservative local excision for resectable partial response
 Option 8 - Additional chemoradiation for unresectable persistent disease
- 5.2.3** The following information will be provided to the RTOG registrar:
- Case number assigned at initial registration
 - Initial patient group (A or B)
 - Response at re-evaluation (*complete response; partial response, resectable; persistent disease, unresectable*)
 - Anticipated date of start of the second phase of treatment
- 5.2.4** A confirmation of re-registration and a new date collection calendar will be sent to the institution. If the patient or investigator deviates from the protocol specified treatment, documentation of this must be submitted to RTOG.
- 5.2.5** If the patient will not continue to the second phase of treatment, the second registration call must still be made; however, the caller will inform the registrar of this so that the case may be marked "discontinued". The caller will supply the original case number and the reason for "discontinuation". The patient will remain on the originally assigned treatment option and data will be submitted according to the original data calendar.

6.0 RADIATION THERAPY

6.1 Dose And Fractionation

- 6.1.1** Treatment shall be administered once daily, with five fractions administered weekly.
- 6.1.2** Each treatment fraction shall consist of a dose of 1.80 Gy administered to each prescription point.
- 6.1.3** For patients with clinically **NODE NEGATIVE** groins, the dose to the inguino-femoral nodes and to the prescription point in the low pelvis shall consist of 45.0 Gy administered in 25 equal fractions of 1.8 Gy delivered over 5 weeks, with 2 cycles of concurrent chemotherapy given synchronous with fractions 2,3,4,5 and fractions 22,23,24,25.
- 6.1.4** For patients with **NODE POSITIVE** groins, the dose to the groins following superficial inguino-femoral node dissection shall consist of 50.4 Gy administered in 28 equal fractions of 1.8 Gy delivered over 5.6 weeks. The dose administered to the prescription point in the pelvis shall consist of 45.0 Gy administered in 25 fractions of 1.8 Gy. The final 3 fractions of 1.8 Gy (*fractions 26,27,28*) shall be administered only to the groin volume and may be delivered employing limited anterior electron or photon ports intended to encompass only the groin node volume while excluding the primary tumor.
- 6.1.5** The dose within a reduced "boost" volume for patients not rendered resectable by non-exenterative, conservative surgery shall be 18.0 Gy administered in 10 equal fractions of 1.80 Gy over 5 days delivered twice daily (*b.i.d.*) with a third cycle of concurrent chemotherapy (*5-FU and MitC*) to commence after the initial two fractions of "boost" radiation.
- 6.1.6** **The inter-treatment interval for patients receiving twice daily "boost" radiation shall be 6 hours or longer, and shall be recorded daily in the treatment chart.**
- 6.1.7** The dose within a reduced volume used as a consolidative treatment for patients achieving a complete clinical response to the initial 45.0 Gy of chemoradiation shall be 9.0 Gy administered in 5 equal fractions of 1.80 Gy over 1 week concurrently with a third cycle of concurrent 5FU commencing after the first consolidative radiation fraction has been administered.
- 6.1.8** In the eventuality that scheduled chemotherapy needs to be delayed because of toxicity (*hematopoietic suppression*), then radiotherapy needs also to be delayed such that treatment may be delivered concurrently. Should acute radiation side effects (*diarrhea, moist desquamation, etc.*) indicate interruption of radiotherapy, then chemotherapy should also be delayed to permit concurrent therapy when radiation resumes. In this protocol, chemotherapy is being employed as a potentiator of local radiation response, therefore every effort must be made to deliver these modalities in a coordinated fashion designed to produce therapeutic synergism.

6.2 Target Volume: (Appendix VI)

- All fields (*photon/electron*) treated require simulator and portal verification on the treatment unit. If electron portals not available, polaroids or simulation films of treatment area should be submitted. Copies of films are to be submitted to RTOG Headquarters.
- 6.2.1** The initial volume for treatment shall encompass the entire vulva and all visible and palpable cancer with a margin of at least 3.0 cm in all directions within tissue.
- 6.2.2** The full length of the vaginal canal will be encompassed for any patient with extension of disease proximal to the hymenal ring.

- 6.2.3** For patients with involvement of the perineal body, anal mucosa or sphincter, or patients whose disease extends lateral to the labio-crural folds, the initial treatment volume will encompass the entire perineum and its lymphatics which course through the upper medial thighs.
- 6.2.4** The INFERIOR BORDER is intended to encompass the entire vulva and adjacent perineal skin and should circumscribe the labia majora with at least 2.0 cm of fall-off to permit use of bolus and effective tissue compensators. In order to confidently encompass the inferior inguinal nodes which may lie along the saphenous vein, it is recommended that the inferior border of the volume intended to include the groin nodes extend at least 10 cm inferior to the middle of the inguinal ligament bilaterally.
- 6.2.5** The LATERAL BORDERS are intended to encompass the entire inguino-femoral node groups (*groins*), and will extend to the anterior superior iliac crest at the lateral extent of the inguinal ligaments.
- 6.2.6** The SUPERIOR BORDER of the treatment volume will be different for patients in the groin node negative and groin node positive treatment assignments:
- 6.2.6.1** For GROIN NODE NEGATIVE patients, the superior border is intended to encompass the lower (*caudal*) external iliac and internal iliac nodes, and is to be placed at the inferior extent of the sacro-iliac joints.
- 6.2.6.2** For GROIN NODE POSITIVE patients, the superior border shall be placed at the L5-S1 interspace.
- 6.2.7** For patients who are not rendered resectable by non-exenterative surgery, the reduced treatment volume ("*boost*" volume) shall circumscribe the initial gross tumor volume with a margin not to exceed 2.0 cm of clinically uninvolved tissue. *The groin nodes shall not be included in the boost volume.*
- 6.2.8** For patients who have achieved a complete clinical response (*CCR*) to the initial 45.0 Gy of chemoradiation, the reduced volume for consolidative chemoradiation shall consist of the initial gross tumor volume.

6.3 Techniques

- 6.3.1** The initial target volume will be treated with anterior and posterior ports employing one of two approved techniques (*Appendix VI*).
- 6.3.2** Patients may be treated with a combination of photons and electrons to avoid excess dose to the femoral necks. A large anterior photon field is designed to encompass the entire treatment volume including both the primary and the nodal volume. A smaller posterior photon field is employed to encompass the primary and low pelvic nodes, but excluding the femoral necks and all but the most medial inguinal nodes. 50% of the central axis dose will be administered from the anterior field, and 50% from the posterior field. The dose contribution to the deep inguino-femoral nodes from the anterior photon field will be calculated at the depth of the anterior wall of the external iliac arteries as they pass under the inguinal ligaments to become the femoral arteries. These depths will be measured from the mandatory pre-registration CT or MRI scan in node negative patients. A limited, repeat post-operative CT or MRI scan to determine depths of the femoral arteries is recommended for patients who have undergone groin node dissections pursuant to the node positive treatment assignment. Anterior electron fields will be employed to deliver sufficient dose to those points to bring the cumulative daily dose to the inguino-femoral nodes to 1.80 Gy. Appropriate electron energy and bolus is to be employed such that the depths of the anterior walls of the external iliac arteries lie at the 90% or higher isodose line, and so that the cumulative dose to the midpoint of the femoral neck shall not exceed 40.0 Gy. (*Appendix 6, Figure A.*)
- 6.3.3** Patients may be treated employing photons alone using a partial transmission central block (*Appendix 6, Figure B*). The anterior photon field encompasses the entire initial target volume including both the primary as well as the inguino-femoral nodes and low pelvis. A dose of 1.80 Gy is prescribed to the deep femoral nodes at the depth of the anterior walls of the external iliac arteries as they pass below the inguinal ligament to become the femoral arteries. These depths shall be determined from the mandatory pre-registration CT or MRI scan for node negative patients. A limited repeat, post-operative CT or MRI scan to determine this depth is recommended for patients who have undergone groin dissections on the node positive treatment assignment. The dose contributed to the midplane separation at the central axis is calculated, and a partial transmission block poured which will attenuate the dose to the midplane central axis to .90 Gy. A posterior photon field corresponding to the area shielded by the anterior partial transmission block is used to deliver an additional .90 Gy to the midplane separation at the central axis. Both the inguino-femoral nodal areas and the point at the midplane separation of the central axis thus absorb 1.80 Gy per daily fraction. The energy of the anterior photon field should be selected such that the cumulative dose to the midplane of the femoral necks shall not exceed 40.0 Gy. It is advantageous to employ a lower energy photon beam for the anterior field (*4-6 MV*) and a higher photon energy for the posterior beam when a treatment machine with dual photon energy capability is available.
- 6.3.4** The dose delivered to a reduced "boost" volume in patients not rendered resectable by non-exenterative surgery, or to patients undergoing consolidative reduced volume chemoradiation following a complete clinical response, may be administered by one of two acceptable teletherapy techniques: A reduced

volume parallel opposed pair of anterior and posterior photon fields may be employed. Alternatively, a direct, en-face perineal electron port may be employed of such energy that D_{max} lies deep to the deepest clinical extension of palpable tumor. Minimum allowable electron energy will be 9 MeV. The volume treated within the boost portals must exclude both the inguino-femoral nodes as well as the femoral heads and necks. Brachytherapy is not to be employed.

6.4 Dose Specifications

- 6.4.1** Dose to the right and left inguino-femoral nodes will be calculated and prescribed to depths determined by the depths of the anterior walls of the external iliac arteries as they pass below the inguinal ligaments to become the femoral arteries. These depth will be determined from the mandatory pre-registration CT or MRI scan. A limited post-surgical CT or MRI scan through the groin areas is recommended to determine femoral artery depth in patients who have undergone superficial groin dissections pursuant to the node positive treatment assignment. The daily fraction size shall be 1.80 Gy to both the right and the left groin nodes.
- 6.4.2** Dose to the pelvis (*initial treatment volume*) shall be calculated and prescribed at the midplane separation of the central axis of the opposed photon beams. Daily fraction size shall be 1.80 Gy delivered to this point.
- 6.4.3** Dose within a reduced "boost" volume or consolidative volume shall be calculated and prescribed at the midplane separation of the central axis when reduced parallel opposed fields are employed. The dose at this point shall be 1.80 Gy per daily fraction.
- 6.4.4** Dose within a reduced "boost" volume or consolidative volume shall be calculated and prescribed to D_{max} when a perineal electron port is the technique chosen.
- 6.4.5** Because of the slope of the vulva and the medial upper thighs, the vulva may receive a higher dose than the dose administered to the prescription points. As vulvar cancer is essentially cancer arising in specialized skin, the use of bolus is encouraged both to provide dose homogeneity and to counter the potential underdosage of portions of the primary tumor occasioned by the use of megavoltage radiation.
- 6.4.6** A vulva dose will be measured with the use of a thermoluminescent dosimeter or equivalent direct dose measuring device placed between the labia minora at the vaginal introitus. This measurement will again be obtained if a reduced volume "boost" or a consolidative volume is subsequently treated in order that a total vulvar dose may be calculated.

6.5 Equipment

- 6.5.1** Megavoltage equipment will be used for all treatment.
- 6.5.2** Minimum photon energy shall be 4 MV. When photon energies higher than 6MV are employed to treat the inguinal areas, bolus or beam spoilers may be required in some thin patients to avoid underdosing superficial groin nodes which might lie in the "build-up" region.
- 6.5.3** Minimum treatment distance shall be 80 cm SAD.
- 6.5.4** Minimum allowable electron energy will be 9 MeV, although energies of 15 MeV, 18 MeV, or higher will often be required to adequately treat the deep femoral nodes.

6.6 Acute Radiation Toxicity

- 6.6.1** Toxicity attributed to radiation effect experienced during radiotherapy or within 90 days of beginning treatment shall be reported using the RTOG Acute Radiation Morbidity Scoring Criteria (*Appendix IV*).
- 6.6.2** Guidelines for the management of vulvar and perineal skin reactions are contained in Appendix VIII.

6.7 Radiation Compliance and Quality Assurance

- 6.7.1** No alteration in dose per fraction or fractionation schedule is permitted.
- 6.7.2** Administration of a cumulative dose of radiation in the initial treatment, consolidative treatment, or "boost" treatment which varies from the protocol specified dose by less than or equal to 10% will be scored a protocol variation/acceptable for purposes of radiation therapy quality assurance and assignment of protocol compliance score.
- 6.7.3** Any of the following will result in mandatory assignment of the case to the category **protocol deviation/unacceptable** for purposes of radiation therapy quality assurance and assignment of protocol compliance score:
- 6.7.3.1** • Failure to treat with either of the approved initial technique options in outlined in Sections 6.3.2 and 6.3.3
 - 6.7.3.2** • Failure to treat with either of the approved techniques for consolidative or "boost" radiation therapy as outlined in Section 6.3.4.
 - 6.7.3.3** • Use of brachytherapy.
 - 6.7.3.4** • Administration of either consolidative or "boost" chemoradiation without formal evaluation of primary tumor response by the attending gynecologic oncologist.
 - 6.7.3.5** • Administration of chemotherapy without radiation in an alternating or staggered fashion will be

scored a protocol deviation/unacceptable.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 Timing: In this protocol, chemotherapy is primarily employed as an enhancer of local radiation effect. *The timing of chemotherapy is co-ordinated with the fraction number of radiotherapy, NOT the calendar day of the study.* Chemotherapy should always be given synchronously with radiation and, whenever feasible, in full dose. A delay of a week for both modalities in order to permit hematologic recovery is preferable to reduction of chemotherapy dose. However, chemotherapy dose reduction should be instituted in preference to a delay in both modalities for longer than a week. In the event that radiation toxicity delays or interrupts scheduled radiation, chemotherapy must also be delayed. Chemotherapy administration without concurrent radiation will be scored a deviation from protocol/unacceptable for purposes of assigning overall protocol compliance score. Mitomycin-C, associated with nausea and vomiting, should be managed with vigorous anti-emetics rather than with treatment interruption or delay.

7.2 Fluorouracil (5FU): 5FU is commercially available in 10 ml. ampules containing 500 mg. It is a fluorinated pyrimidine which resembles the natural pyrimidine uracil except that a fluorine atom replaces a hydrogen atom at the 5 position. 5FU interferes with the synthesis of DNA by blocking the methylation of deoxyuridylic acid to thymidylic acid, as well as inhibiting synthesis of RNA. Thymidine deficiency may lead to unbalanced growth and cell death. The precise cellular mechanism of radioenhancement is not known, but the clinical observation is that 5FU enhances acute radiation response in cycling cell populations, both normal and malignant.

7.2.1 5FU shall always be administered as a continuous intravenous infusion in D5W or 1/2 NS. The rate of infusion shall remain constant over 96 hours.

7.2.2 The first 5FU infusion shall commence after the first fraction of radiation, and shall consist of 1000 mg/m²/24 hrs. for 96 hours concurrent with radiation fractions 2,3,4,5 as the cumulative radiation dose to the initial large volume increases from 1.8 Gy to 9.0 Gy. The maximum 5FU dose per 24 hours shall be 2000 mg, and the total dose shall not exceed 8000 mg in 96 hours.

7.2.3 The second 5FU infusion shall commence after fraction 21 of radiation and will be delivered concurrently with fractions 22,23,24,25 of radiation as the cumulative radiation dose to the initial large volume increases from 37.8 Gy to 45.0 Gy. Dose reduction for hematopoietic suppression, if necessary, should be accomplished by reducing the amount of drug infused and not the duration of the infusion (*Sec. 7.4*). Major hematopoietic suppression will require that radiation and chemotherapy be delayed 1 week to permit marrow recovery. If persistent hematopoietic suppression indicates 5FU dose reduction, this will be accomplished by administration of 5FU at 750 mg/ m²/24 hrs. for 96 hours, with a maximum of 1500 mg in 24 hours and a total dose of 6000 mg for the 96 hour infusion.

7.2.4 Should a third 5FU infusion be indicated, this shall be accomplished concurrently with the last eight fractions/4 days of reduced volume BID "boost" radiation (*fractions 28-35 for node negative patients or fractions 31-38 for node positive patients*) or the last four fractions of daily consolidative radiation (*fractions 27-30 for node negative patients and fractions 30-33 for node positive patients*) and shall be administered at the same infusion dose schedule as utilized for the second course of 5FU.

7.3 Mitomycin-C (MitC): Mitomycin-C is commercially available in vials containing 5 or 20 mg. Mitomycin-C inhibits the synthesis of DNA by inducing cross-linkages between guanine and cytosine, and may effect RNA and protein synthesis.

7.3.1 MitC will be given as an intravenous bolus concurrently with fractions 2 and 22 of the initial course of large volume radiation. The dose of MitC shall be 10 mg/m², with the maximum dose per administration to be 20 mg.

7.3.2 MitC should always be administered via the tubing of a free flowing infusion to minimize the potential hazard of extravasation. Treatment procedures for Mitomycin-C extravasation are found in Appendix VIII.

7.3.3 Significant hematopoietic suppression will require that radiation and chemotherapy be delayed to permit marrow recovery. If after a 1 week delay blood counts remain suppressed, reduced dose MitC shall be administered at 7.5 mg/m², with the maximum second dose to be 15 mg. Severe hematopoietic suppression will require dose delay, reduction, or deletion according to the table in Section 7.4.

7.3.4 Major, life-threatening hematopoietic suppression (*grade 4 toxicity*) will mandate deleting the second dose of MitC.

7.3.5 If a reduced volume "boost" is to be irradiated in a patient with an inadequate initial response to render their primary cancer resectable by conservative surgery, a third and final dose of MitC shall be

administered concurrently with fraction 28 of radiation for node negative patients and fraction 31 of radiation for node positive patients. The third MitC dose is to be given on the second day of "boost" radiotherapy in conjunction with starting the third 5FU infusion. The MitC dose shall be the same as employed for the second course of chemotherapy. If MitC was not administered with the second course of chemotherapy, it shall not be administered with the third course of chemotherapy. Hematopoietic suppression, as described in the table in Section 7.4, may indicate a one week delay in delivery of the third cycle of chemoradiation, but "boost" radiation should not be delayed more than one week due to circulating counts inadequate for MitC administration, and chemoradiation may be accomplished with 5FU alone should inadequate circulating counts persist after a one week delay.

7.3.6 Anti-emetic medication is highly recommended before, during, and after MitC administration. Ondansetron, Granisetron, Metoclopramide, Lorazepam, Dexamethasone, Chlorperazine, and Diphenhydramine Hydrochloride may be helpful agents.

7.4 Chemotherapy Dose Modification

7.4.1 Blood counts prior to second and third course of chemotherapy:

ABSOLUTE NEUTROPHILS	PLATELET COUNT	5FU DOSE	MIT-C DOSE
> 1500	> 100,000	Full Dose	Full Dose
> 1500	≤ 100,000	Delay 1 Wk	Delay 1 Wk
≤ 1500	> 100,000	Delay 1 Wk	Delay 1 Wk
≤ 1500	≤ 100,000	Delay 1 Wk	Delay 1 Wk

7.4.2 Blood counts after 1 week delay:

ABSOLUTE NEUTROPHILS	PLATELET COUNT	5FU DOSE	MIT-C DOSE
> 1500	> 100,000	Full Dose	Full Dose
1000-1500	> 100,000	Full Dose	7.5 mg/M ²
1000-1500	75-100,000	750 mg/M ² /24hrs	Delete
500-1000	< 75,000	Delay Call Study Med. Onc. Chair	Delete

7.5 Supportive Measures and Monitoring During Chemoradiation

7.5.1 Patients are to be seen at least weekly by their radiation oncologist during chemoradiation. This will entail physical examination of the perineal and vulvar skin as well as routine monitoring for chemoradiation acute side effects.

7.5.2 Complete blood counts are to be obtained at least once weekly during chemoradiation on all patients. Blood counts are advised to be obtained on Thursdays such that results will be known prior to weekends. Blood counts may be obtained more frequently at the discretion of the treating physicians. Monitoring of blood counts should continue weekly for at least 4 weeks following the final cycle of chemotherapy, or longer until nadir neutrophil and platelet counts have been passed.

7.5.3 In the event of either severe diarrhea, or nausea and emesis with diminished oral intake and absorption, dehydration and electrolyte imbalance may ensue. Weekly electrolytes (*renal panel*) are recommended, but not required to be obtained at the same time as the weekly blood counts.

7.5.4 Hematocrit should be maintained at 30% or higher throughout the course of chemoradiation. Either transfusion or erythropoietin may be utilized at the discretion of the treating physicians, and use of either of these supportive modalities will be communicated to RTOG Headquarters as part of treatment summary reporting.

7.5.5 Use of granulocyte colony stimulating factors for neutropenia shall be at the discretion of the treating physician. Use of such agents must be communicated to RTOG Headquarters on the data forms.

- 7.5.6 Use of prophylactic antibiotics for simultaneously occurring severe neutropenia and moist perineal desquamation shall be at the discretion of the treating physicians, but must be communicated to RTOG Headquarters on the data forms.
- 7.5.7 Use of antibiotics or hospitalization for febrile neutropenia will be at the discretion of the treating physicians but must be communicated to RTOG Headquarters as part of treatment summary reporting.
- 7.5.8 In addition to being reported to RTOG Headquarters, **all grade 4 or 5 hematologic toxicities must be personally reported to the medical oncology study Chair by the patient's attending medical oncologist.**
- 7.5.9 Chemotherapy toxicity reporting will be done using the Cooperative Group Common Toxicity Criteria (*Appendix IV*).
- 7.5.10 Skin care of the perineum and vulva shall be under the direction of the radiation oncologist and nursing staff experienced with management of acute radiation dermatitis and moist desquamation. Guidelines in Appendix VII are intended to be helpful suggestions rather substitutes for regimens used in member institutions.

7.6 Adverse Drug Reaction Reporting

- 7.6.1 The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol which uses commercial agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:
- 7.6.1.1 Any ADR which is both serious (*life threatening, fatal*) and unexpected.
- 7.6.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- 7.6.1.3 Any death on study if clearly related to the commercial agent(s).
- 7.6.1.4 Acute myeloid leukemia (*AML*). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.
- 7.6.2 The ADR report should be documented on Form FDA 3500 (*Appendix V*) and mailed to the address on the form, to RTOG Headquarters and to:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone (301) 230-2330
available 24 hours
fax 301-230-0159**

7.7 Chemotherapy Compliance And Quality Assurance

- 7.7.1 Miscalculation or misadministration of either or both agents in a quantity less than or equal to a 10% variation in total protocol dose will constitute a variation from protocol/acceptable for purposes of medical oncology quality assurance review and assignment of overall protocol compliance score.
- 7.7.2 Any of the following deviations from protocol will trigger mandatory assignment of the case to the category of **protocol deviation/unacceptable** for purposes of medical oncology quality assurance review and overall protocol compliance score:
- Failure to complete a cycle of planned chemotherapy once initiated.
 - Miscalculation or misadministration of either chemotherapeutic agent by an amount greater than 10% of the protocol specified dose.
 - Administration of protocol drugs separate from the administration of radiation therapy (*in a non-concurrent, sequential, or alternating fashion.*)
 - Administration of non-protocol cytotoxic agents except after failure of protocol therapy (*recurrence*).
 - Failure to observe appropriate dose reduction as specified in Section 7.4.

8.0 SURGERY

8.1 Patients With Clinically Negative Groins

Initial surgery is intended to be for diagnostic purposes only and may consist of biopsies at one or more sites to establish the diagnosis and the extent of the primary cancer. Excisional biopsy of at least one lymph node from each groin which is detected to harbor a palpable or CT identified node larger than 1.0

cm. is a pre-registration study requirement. Operative and pathology reports from excisional biopsies will be sent to RTOG Headquarters. This excisional biopsy is for diagnostic purposes only and is not intended to be a therapeutic dissection. For patients without nodal enlargement greater than 1.0 cm, no lymph node biopsy is required. For patients with clinically negative groins there shall be no further therapeutic surgery directed to the inguino-femoral node areas (*groins*) except as salvage therapy for histologically confirmed cancer progression in the nodes.

8.2 Patients With Histologically Positive Groins

Patients with histologically confirmed metastasis to groin nodes (*unilateral or bilateral*) will undergo initial bilateral superficial inguino-femoral node dissection with the intent to surgically remove all groin nodes superficial to the cribriform fascia. If there are palpable or radiographically identified nodes larger than 1.0 cm below the cribriform fascia, such enlarged nodes should be surgically removed as well and submitted as a separate specimen for pathologic study. However, a complete therapeutic deep groin node dissection is not intended. Surgical removal of enlarged lymph nodes superior to the inguinal ligament (*palpated at the time of surgery*) is permitted. If such nodes are removed they must be identified and submitted as a separate specimen for pathologic study. If vulvar lymphatic mapping (*Appendix IX-B*) is performed and indicates that the so-called "sentinel node" lies below the cribriform fascia, it should be removed even if not palpably enlarged. If such nodes are removed they must be identified and submitted as a separate specimen for pathologic study. The sentinel node(s) identified by lymphatic mapping should be so identified and submitted for pathologic study as a separate specimen. Copies of operative and all pathology reports shall be forwarded to RTOG Headquarters.

8.3 Evaluation for surgery after preoperative chemoradiation should be made 12-14 days after completion of the second course of chemotherapy and 45.0 Gy. If, in the judgement of the attending gynecologic oncologist, the primary cancer is sufficiently reduced to permit surgical removal without functional compromise of midline structures (*bladder, ano-rectum, vagina or clitoris*), conservative local excision of residual tumor should be undertaken. Biopsy confirmation of residual disease is not required prior to excision. Conservative local excision is intended to encompass the volume of residual palpable abnormality with a margin of approximately 1.0 cm, and is not intended to remove all areas of original involvement. Copies of operative and pathology reports shall be sent to RTOG Headquarters.

8.4 Conservative local excision should be undertaken when any areas of moist desquamation of vulvar or perineal skin have re-epithelialized, and when the patient has passed through the nadir of hematopoietic suppression. It is anticipated that conservative local excision should be feasible 3-6 weeks after completion of preoperative chemoradiation.

8.5 For patients with clinically negative groins there shall be no therapeutic surgery directed to the inguino-femoral node areas (*groins*) at the time of conservative surgery for the primary cancer. Groin dissection shall not be undertaken except as salvage therapy for histologically confirmed cancer progression in the nodes.

8.6 If, in the joint judgement of the attending gynecologic oncologist and radiation oncologist, a complete clinical response (*CCR*) has been achieved by the initial 45.0 Gy and two courses of chemotherapy, surgery may be omitted and an additional third course of consolidative chemoradiation shall be administered consisting of 5-FU infusion (*Section 7.2.4*) concurrent with 9.0 Gy prescribed to a reduced target volume (*Sections 6.1.7, 6.2.8, and 6.3.4.*) Biopsy to confirm complete response is recommended but not required.

8.7 If, in the judgement of the attending gynecologic oncologist, the response of the primary tumor to the initial 45.0 Gy and two courses of chemotherapy is not sufficient to permit conservative local excision (*Section 8.3*), an additional course of "boost" chemoradiation shall be administered consisting of 5-FU (*Section 7.2.4*) and MitC (*Section 7.3.5*) concurrent with 18.0 Gy prescribed to a reduced target volume (*Sections 6.1.5, 6.1.6, 6.2.7, and 6.2.8.*)

8.8 Administration of either consolidative or "boost" chemoradiation without formal evaluation of primary tumor response by the attending gynecologic oncologist will constitute mandatory assignment of protocol deviation/unacceptable case status for purposes of radiation therapy and surgical quality assurance review and overall protocol compliance score.

8.9 Surgical Treatment of Persistent Disease

The patients who are anticipated to be entered on this study will constitute a population whose only common characteristics are expected to be gender and malignant diagnosis. They are likely to be diverse with respect to age and a variety of co-existing health problems. Persistent tumor, clinically suspected and biopsy proven at six or more weeks after completion of all chemoradiation, is assumed to represent viable, clonogenic cancer. Locally persistent tumor may be amenable to surgical salvage. Because of the heterogeneity of the patient population, whether or not surgical resection of persistent disease is undertaken, and the scope of such surgery, if undertaken, will be left to the patient and her physicians to

decide. However, therapeutic inguino-femoral node dissection will not be carried out unless there is histologic verification of groin node relapse. Surgical dissection of the inguino-femoral nodes after chemoradiation in the absence of histologic verification of groin relapse will constitute a mandatory assignment of protocol deviation/unacceptable status for purposes of surgical quality assurance review. Copies of operative and pathology reports from any surgical treatment for persistent disease will be forwarded to RTOG Headquarters.

8.10 Surgical Treatment Of Recurrent Disease

Surgical therapy of recurrent disease, after a period of complete clinical cancer clearance, will depend on the location and extent of recurrence. Due to the heterogeneity of the patient population who are anticipated to be entered in this protocol, the extent of any surgical salvage therapy for recurrent primary disease will be left for the patient and her physicians to determine. However, therapeutic inguino-femoral node dissection will not be carried out unless there is histologic verification of groin node relapse. Copies of operative and pathology reports from any salvage therapy must be forwarded to RTOG Headquarters.

8.11 Surgical quality control will be conducted by surgical chairpersons by review of all operative reports and pathology reports required to be forwarded to RTOG Headquarters.

9.0 OTHER THERAPY

9.1 Treatment Of Recurrent Disease/Salvage Therapy

9.1 No other therapies apply except supportive treatment.

9.2 Following completion of protocol therapy, no additional anti-neoplastic treatment is allowed until confirmation of failure of protocol therapy, or development of a second primary cancer.

9.3 Administration of additional surgery, radiation, or chemotherapy without documentation of failure of protocol therapy will constitute a **deviation from protocol/unacceptable** case assignment for purposes of overall protocol compliance score.

9.4 The patients who are anticipated to be entered on this study will constitute a population whose only common characteristics are expected to be gender and malignant diagnosis. They are likely to be diverse with respect to age and a variety of co-existing health problems. Further complexity is added by the probability that some recurrences will be local (*vulva, vagina, perineum*), some regional (*groin or pelvic nodes*), some distant, and others multi-focal. Because of this diversity, decisions concerning salvage or palliative therapies are to be negotiated between the patient and her physicians, and will not be specified by this protocol. However, medical interventions subsequent to documentation of recurrence are required to be reported to RTOG headquarters, and patients must be followed for life. Investigators are expected to appreciate that potentially curative salvage surgical therapy may be appropriate for some forms of recurrence, and to act accordingly.

10.0 PATHOLOGY

10.1 Pathology reports from initial biopsies, needle aspirations of metastatic nodes, excisional biopsies of groin nodes larger than 1.0 cm, superficial groin dissections from patients with initially positive nodes, and conservative local excisions of the primary cancer after chemoradiation will be forwarded to RTOG Headquarters:

**Pathology Coordinator
RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107
215/574-3192**

10.2 Pathology reports from any biopsies documenting loco-regional recurrence, groin recurrence, or distant metastatic spread will be forwarded to RTOG Headquarters.

10.3 Pathology reports from salvage surgeries for persistent or recurrent disease will be forwarded to RTOG Headquarters.

10.4 Pathology reports from the initial biopsy confirming presence of invasive cancer should comment on the grade (*well differentiated, moderately differentiated, poorly differentiated*) and the presence or absence of endothelial-lined or vascular space invasion.

10.5 Patients with cancer other than epidermoid/squamous cancer of the vulva are not eligible for this study. Patients with the verrucous variant of squamous cancer are not eligible for this study (*Section 3.1*)

10.6 Pathology reports from inguinal node dissections in patients with histologically confirmed node involvement should specify both the number of nodes removed and studied as well as the number of nodes involved with metastatic disease.

10.7 Pathology reports for surgical removal of the primary tumor after chemoradiation should comment on the width of the surgical margins (*in millimeters*) both circumferentially (*laterally*) and deep.

10.8 Central pathology review (*slides or blocks*) may be performed.

10.9 Central Tissue Repository (optional)

10.9.1 Patients appropriately entered on this study may choose to permit submission of tissue to the RTOG Central Tissue Repository. Participation in the Central Tissue Repository program is encouraged, but is not required for participation in this treatment protocol.

10.9.2 A minimum tissue requirement of one (1) paraffin block of untreated primary tumor is to be submitted to the RTOG Central Tissue Repository.

10.9.3 Submission of at least one paraffin block of nodal tissue containing metastatic cancer is additionally required from patients who are assigned to treatment commencing with superficial inguino-femoral node dissection (*node positive patients*).

10.9.4 The institutional pathologist must be informed that the paraffin block (s) will be retained by the RTOG Central Tissue Repository, and that the tissue is being retained with the patient's permission.

11.0 PATIENT ASSESSMENTS

11.1 Assessment Schedule

ASSESSMENT	PRE	FOLLOW-UP MONTH													
	= REG	3	6	9	12	16	20	24	30	36	42	48	54	60	72
Initial/Interval History & General Physical ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁱ
Pelvic Examination ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁱ
Karnofsky Score ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁱ
Clinical Photography ^d	X			X			X		X		X		X	X ⁱ	
PA & LAT. CXR ^f	X		X	X			X		X		X		X		
Abdominal/Pelvic CT or MRI ^g	X														
CBC/Differential	X	X ^h													
Chemistry Panel	X	X ^h													
Late Effects Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X ⁱ	

- a. Each follow-up visit will consist of an interval history and will report on the patients urinary bladder and bowel habit and whether or not the patient is sexually active.
- b. The pelvic and general physical exam should assess for leg edema, pedal and femoral arterial pulses, palpable groin nodes, the severity of late radiation stigmata in the skin of the vulva an perineum, radiation effects in the vagina, and strength of the anal sphincter. Examination should assess the patient for recurrent disease in each groin, on the vulva and perineum, and distantly. Loco-regional recurrences will be reported as outside the initial treatment volume, within the initial treatment volume, within the consolidative treatment volume, or within the "boost" treatment volume.
- c. Appendix II
- d. Color clinical photographs shall be obtained prior to treatment, in annual follow-up to document late normal tissue effects, and at the time of any loco-regional recurrence
- e. Appendix IV.
- f. At 6, 12, 24, 36, 48, 60 months or at the time of failure at any site.
- g. Must be repeated at the time of failure at any site. CT or MRI may be used at the preference of the investigator.
- h. May be monitored sequentially if abnormal. Need not be repeated if normal or baseline at 3 month follow-up.
- i. Annual surveillance continues for life.

11.2 Patients will be evaluated at intervals of 3 months for the initial year following the completion of all therapy. Follow-up will be every 4 months for the subsequent year (*year 2*), then every 6 months for the subsequent 3 years (*years 3-5*). Thereafter, follow-up will be annual for life.

11.3 Each follow-up visit will consist of an interval history and will report on the patients urinary bladder and bowel habits and will include assessment of whether or not the patient is sexually active. Each follow-up visit will record the patient's Karnofsky Performance Score.

11.4 On the occasion of each follow-up visit, a general physical exam shall be performed, and a thorough pelvic examination. The physical exam should assess the presence or absence of leg edema, the integrity

of pedal and femoral arterial pulses, the presence of palpable groin nodes, the presence and severity of late radiation stigmata in the skin of the vulva and perineum, radiation effects in the vagina, and strength of the anal sphincter. The examination should assess the patient for recurrent disease in each groin, on the vulva and perineum, and distantly. Local-regional recurrences will be reported as outside the initial treatment volume, within the initial treatment volume, within the consolidative treatment volume, or within the "boost" treatment volume.

- 11.5** Clinical photographs of residual vulva and perineum are required in all patients annually after completion of therapy. Clinical photographs should be obtained at the time of local recurrence to document whether recurrence is in-field, marginal, or out-of-field with respect to both the initial radiation target volume and possible reduced volumes used for "boost" or consolidative therapy.
- 11.6** Patients suspected to have local recurrence in the vulva, in the vagina, or on the perineum shall have this verified by directed biopsy. Patients suspected to have inguino-femoral node recurrence must have this confirmed by fine needle aspiration or open biopsy. Any groin failure must be reported personally by the attending radiation oncologist to the study Surgical Chair and the study Radiation Therapy Chair in addition to RTOG Headquarters.
- 11.7** At the time of any documented recurrence, the patient shall undergo a pelvic examination, PA and lateral chest radiography, and an abdomino-pelvic CT or MRI scan.
- 11.8** During routine surveillance follow-up, a PA and lateral chest radiograph is required at 6 months, 12 months, 24 months, and then annually until year 5.
- 11.9** A complete blood count and chemistry panel is required at the time of the initial 3 month follow-up. Unless persistent abnormalities are detected which require treatment or repeat determinations, no further blood tests will be required.
- 11.10** At the discretion of the treating physicians, additional follow-up assessments may be performed as clinically indicated, but more intensive testing or surveillance is not required by the clinical investigation.
- 11.11** Late effects in normal tissues within the irradiated volume will be reported using the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (*Appendix IV*).

12.0 DATA COLLECTION

12.1 Summary of Data Submission

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

<u>Item</u>	<u>Due</u>
Medical Oncology Treatment Planning Form (M2)	Within 1 week of study entry
Demographic Form (A5)	Within 2 wks of study entry
Initial Evaluation Form (I1)	
Diagnostic Pathology Report (P1)	Within 1 week of start of RT
Photograph of Lesion (B1)	
<u>Preliminary Dosimetry Information:</u>	
RT Prescription (Protocol Treatment Form) (T2)	
Films (<i>simulation and portal</i>) (T3)	Within 4 weeks of study entry
Calculations (T4)	
PreTreatment CT/MRI Scan (C1) and Report (C3)	
<u>Central Tissue Repository</u> (<i>see Section 10.9</i>)	Within 4 weeks of study entry
Pathology Report (P6)	
Pathology Blocks (P7)	Within 1 week of RT end
Radiotherapy Form (T1)	
<u>Final Dosimetry Information:</u>	
Daily Treatment Record (T5)	
Isodose Distribution (T6)	

To guard against possible eligibility and incomplete data problems, we add nine patients for a **final sample size of 99**. Since the frequency of positive groin nodes has ranged from 21% to 34.5%,³⁴ we expect to see more node negative patients in the study, and separate estimates of the groin relapse rate for the two nodal groups will be calculated. As long as the number of groin relapses is eight or less in the 90 eligible patients, we can say that the relapse rate is not statistically significantly worse than 5% (*at the 5% significance level*), because, if the true relapse rate is 5%, then the probability of observing 8 or more groin failures is 8.1% (*for 9 or more, 3.6%*).

13.3 Accrual

Vulvar cancer is a rare disease. RTOG has no recent experience in accruing patients to studies of vulvar cancer. However, from a survey of our member institutions, we expect to finish the accrual of 99 patients within 3 years. If after two years less than 40 patients are entered, the feasibility of the study will be reevaluated by the Research Strategy Committee.

13.4 Analysis Plan

13.4.1 Interim Analysis and Monitoring

Interim reports will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim report will contain information about the patient accrual rate with a projected completion date for the accrual phase, data quality, compliance rate of treatment delivery, distribution of important prognostic baseline variables and the frequencies and severity of the toxicities. Modifications in treatment delivery and quality control may be recommended based on these interim reports. When serious problems are found, suspension of accrual will be recommended.

The number of groin relapses will not be contained in the interim reports, but it will be monitored closely. By the statistical considerations in Section 13.2, when the chance is very good that we will end up with 9 or more two year groin relapses we will recommend suspension and possibly early stopping of the trial. Specifically, the following rules have been set up: If 3 groin failures have been observed before or when 33 patients have been entered, the trial will be suspended for one year pending review of all patients affected and accumulation of further follow-up data. If one or none groin relapse is observed during the suspension period, the trial will be recommended to reopen with possible modifications of the protocol, otherwise early stopping will be recommended. *Without* this suspension, the same process, i.e., suspension for one year followed by reopening or early stopping depending upon whether > 1 more groin failure is observed, will be initiated if 5 groin relapses have been observed before or when 66 patients have been entered. *With* the first suspension and the decision to reopen, early stopping of the trial will be recommended if 7 groin relapses have been observed before or when 66 patients have been entered.

13.4.2 Analysis for Reporting the Initial Treatment Results

The initial full scale analysis will be done approximately two years after the entry of the last patient. All the endpoints listed in Section 13.1 will be analyzed in detail. Acute toxicities and late effects in normal tissues will be reported using the RTOG acute and late toxicity scales.

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APPENDIX I

RTOG 96-12

PHASE II STUDY OF CHEMORADIATION IN PATIENTS WITH LOCALLY EXTENSIVE EPIDERMOID CARCINOMA OF THE VULVA.

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I have been diagnosed as having a locally spread cancer of the vulva which may involve the lymph nodes (*glands*) in my groin areas. At this time, there does not appear to be any cancer in other parts of my body. The usual surgical treatment of this disease involves removal of all tissue to which the cancer directly has spread as well as all the lymph glands in both groin areas. When vulvar cancer is locally advanced, such surgery may require removal of all, or major portions of, one or more of the anus and rectum, the urethra (*tubes for urination*) and bladder, the clitoris and vagina.

Removal of the anus or rectum implies creation of a permanent colostomy (*an opening or "stoma" on the abdomen to collect fecal material/stool*). Removal of the urethra or bladder implies creation of a urinary diversion (*an opening or "stoma" in the abdominal wall through which urine is collected through a catheter or in a bag*). Removal of the clitoris or a significant portion of the vagina may diminish sexual enjoyment or make vaginal sexual intercourse impossible. Removal of the lymph nodes in the groins may result in long term swelling (*lymphedema*) of the legs with some decrease in mobility. Even with such extensive surgery, post-operative radiation is often advised to sterilize microscopic cancer cells which may not have been fully removed.

Research suggests that radiation therapy and chemotherapy (*drug treatment*), administered at the same time, may shrink some vulvar cancers to the point where they may be removed by less extensive surgical procedures or may be cured without the need of surgery. Preliminary evidence suggests that radiation therapy directed to the groin nodes along with chemotherapy at the same time may be as equally effective as surgery, and less damaging than surgery when used in the treatment of patients with cancers of the vulva. When there is spread of the cancer to the groin lymph nodes, use of chemotherapy and radiation directed to the groins after limited surgical removal of involved lymph nodes may possibly cause fewer long term complications than the more extensive surgery conventionally used.

The Radiation Therapy Oncology Group, a research organization for which the National Cancer Institute has oversight and funding responsibilities, is evaluating the effectiveness of radiation combined with simultaneous chemotherapy as partial or total treatment for patients with locally extensive vulvar cancer. The study is investigating whether, for carefully selected patients, chemotherapy delivered at the same time with radiation therapy to the groin node areas, is an effective alternative to extensive surgical dissection of the groin areas. For other patients, in whom there is established spread of the cancer to lymph nodes in the groin, this study will determine if less extensive surgery than is conventionally used, coupled with radiation and chemotherapy, will be as effective as radical groin surgery, but with a lower chance of long term treatment complications. This study will also assess how often chemoradiation can shrink extensive vulvar cancers to allow limited, conservative surgery without removal of functionally important normal tissues, and how often chemoradiation may cure vulvar cancer when conservative surgery is not possible.

DESCRIPTION OF PROCEDURES

As part of my evaluation concerning whether it is medically appropriate for me to be registered on this study, I will be asked to have a chest X-ray, routine blood counts and blood chemistry determinations (*which will involve obtaining small blood samples with a needle from a vein*) and a CT scan or MRI scan of my abdomen and pelvis. I will undergo a complete physical examination, and photographs of the cancer (*not including by face or name*) will be obtained for purposes of the

study.

These tests are commonly used as standard assessments of patients with locally extensive vulvar cancer prior to treatment, even when patients are not participating in clinical research. If I am willing to be registered on the study, I will be assigned to one of two similar treatment programs based upon whether or not there is spread of the cancer to involve one or more lymph nodes in my groin area:

1. Treatment for Patients Without Lymph Node Spread

I will undergo daily radiation treatments (*Monday through Friday*) for five weeks (*25 treatments*). Chemotherapy (*cancer drug treatment administered through a vein*) will be given along with radiation during the first and fifth weeks of radiation. On each occasion the chemotherapy will be given over four days, possibly in the hospital. The chemotherapy used will be two drugs called 5-Fluorouracil (*5FU*) and Mitomycin-C. 12-14 days after completing initial treatment, I will undergo repeat evaluation by my radiation oncologist and gynecologist which will include a physical examination to assess cancer shrinkage and to determine how my treatment will be completed. Limited biopsies may be performed to aid in this evaluation. Depending on the degree of shrinkage of the cancer, I will be advised to undergo additional treatment in one of three ways:

- 1) If all detectable cancer has disappeared, I will have five additional radiation treatments in one week aimed at a limited area of tissue together with a third course of chemotherapy with 5FU alone.
- 2) If there has been sufficient cancer shrinkage to permit conservative local surgical excision without functionally damaging important normal tissues, such surgery will be carried out 3 to 6 weeks after chemotherapy and radiation were completed.
- 3) If there has not been sufficient cancer shrinkage to allow conservative local excision, I will get an additional week of 10 radiation treatments given twice daily (*separated by 6 or more hours*) in conjunction with a third course of chemotherapy consisting of 5FU and Mitomycin-C.

2. Treatment For Patients With Lymph Node Spread

If I am willing to participate in the study, I will first undergo surgery to remove the superficial lymph nodes in both groin areas. The surgery will remove all enlarged lymph nodes in the groin areas, but will not remove all of the lymph nodes.

My surgeon may ask me to undergo the procedure known as Intraoperative Lymphatic Mapping. This procedure is not part of the treatment in this study. Participation is voluntary. I may decline to participate in Intraoperative Lymphatic Mapping and still participate in the rest of the study. For mapping, I will undergo limited injection of a small quantity of blue dye (*approximately one fourth of a teaspoonful*) in the skin directly next to the cancer on both sides of the cancer. The injection of dye will be done at the time of my planned surgery, immediately prior to the surgical removal of my groin lymph nodes, and will be done under anesthesia. Therefore, there will be no additional discomfort associated with the dye injection. The dye will be used to identify the first lymph nodes to process lymphatic drainage from the vulva in order that they may be removed and studied microscopically separately from the other lymph nodes in the groins. Permanent discoloration of the skin is unlikely but not impossible. Participation in this additional study is very unlikely to change the surgery performed or the side effects or complications of that surgery. No additional studies are required to participate in this additional research, and I will not have any additional expense. The dye utilized is commonly used in diagnostic radiology procedures known as lymphangiograms. Adverse or allergic reactions to the dye are very unusual, although development of a local rash or hives (*an itchy, generalized skin reaction*) is possible. More serious, potentially dangerous allergic reactions are possible, but very unlikely.

Following surgical removal of the superficial lymph nodes in the groin areas I will then undergo daily radiation treatments (*Monday through Friday*) for five weeks and 3 days (*28 treatments*). Chemotherapy (*cancer drug treatment administered through a vein*) will be given along with radiation during the first and fifth weeks of radiation. On each occasion the chemotherapy will be given over four days, possibly in the hospital. The chemotherapy employed will be two drugs called 5-Fluorouracil (*5FU*) and Mitomycin-C. 12-14 days after completing initial treatment, I will undergo repeat evaluation by my radiation oncologist and gynecologist which will include a physical examination to assess cancer shrinkage and to determine how my treatment will be completed. Limited biopsies may be performed to aid in this evaluation. Depending on the degree of response (*shrinkage of cancer*) I will be advised to undergo additional treatment one of three ways:

- 1) If all detectable cancer has disappeared, I will have five additional "consolidative" radiation treatments in one week

targeted to a limited volume of tissue in conjunction with a third course of chemotherapy with 5FU alone.

- 2) If there has been sufficient cancer shrinkage to permit conservative local surgical excision without functionally damaging important normal tissues, such surgery will be carried out 3 to 6 weeks after chemotherapy and radiation were completed.
- 3) If there has not been sufficient cancer shrinkage to allow conservative local excision, I will undergo an additional week of 10 radiation treatments given twice daily (*separated by 6 or more hours*) in conjunction with a third course of chemotherapy consisting of 5FU and Mitomycin-C.

Laboratory/Clinical Correlative Studies in Vulvar Cancer

At the time of diagnosis, some of my cancer was removed. As is standard practice, this tissue went to a pathology department for study under the microscope and for diagnosis. After that process was completed, some of this tissue remained in the pathology department in storage. If I consent to participate in this research, some of this stored tissue will be sent to the Radiation Therapy Oncology Group to be used in laboratory studies which are looking for special "markers" associated with cancers which may be useful, in the future, to predict which cancers will be likely to respond well to treatment, and which therapies have the most chance for success.

Follow-Up After Completing Treatment

Following completion of all treatment, I will be seen in follow-up every 3 months for one year, every 4 months per 2 years, then every 6 months for the two more years, and annually thereafter for life. During each follow-up assessment, an interval history will be obtained and a physical examination performed. A chest X-ray will be obtained every 6 months for two years, and annually for three years thereafter. Photographs of the treated area will be obtained annually after the completion of treatment.

Additional studies may be obtained as clinically indicated or at such time as the cancer may recur, but are not part of routine surveillance as specified in the research study.

All of these follow-up tests and examinations are considered routine even for patients treated for vulvar cancer who are not participating in clinical research.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. There are side effects and possible hazards associated with surgery, radiation, and chemotherapy, even when administered alone. Using these cancer treatment modalities in combination with each other may increase the risk of some types of side effects and complications. In addition to the side effects described below, there is always the risk of very uncommon or previously unknown side effects or complications occurring.

SURGERY: Possible risks include blood loss, infection, non-healing of tissues, scarring and pain, as well as rare risks associated with administration of anesthetic agents such as allergic reactions. Rarely, blood loss is sufficiently extensive to cause a need for blood transfusion.

RADIATION THERAPY: Radiation treatments may cause fatigue, nausea, loss of pubic hair, irritation of the skin of the vulva and groin areas causing redness and possibly extensive, painful temporary blistering. Irritation of the urinary bladder may occur, causing a need to urinate frequently and possible burning symptoms associated with passing urine. Radiation therapy may cause an increased frequency of bowel movements and diarrhea, and may cause hemorrhoidal symptoms in some patients. Vaginal dryness and itching may occur.

Pelvic radiation therapy will cause loss of ovarian function in pre-menopausal women and will result in permanent infertility (*inability to have a child*). Pelvic radiation will cause fetal loss (*abortion*) or damage to unborn children in pregnant patients. **If I am pregnant or possibly pregnant, I must inform my doctor of this prior to proceeding with treatment.** There is conclusive medical information showing that this treatment would be harmful to an unborn child. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. This requires that blood be drawn by venipuncture within 7 days prior to the study. The results will be made available to the study participant prior to the initiation of this study.

Most radiation side effects resolve fully within 6 weeks of completion of treatment, however long-term effects may be seen in normal tissues. Radiation scarring in the skin of the vulva and perineum can produce areas of contracted or tender skin which can impair the ability to have vaginal sexual relations. Narrowing and dryness of the vagina may occur which can

cause painful intercourse, although use of a vaginal dilator and vaginal lubricants will prevent this in many patients. Rarely, radiation may cause long-term damage to the urinary bladder or rectum resulting in bleeding and irritative symptoms. Uncommonly, radiation may cause fracture of pelvic bones or bones of the hip joints (*femurs*) which can require surgery to repair. Swelling of the legs and injury of the blood vessels or nerves supplying the legs are very rare complications of radiation treatment when radiation is given alone.

Swelling of the legs is more common when radiation is given following surgical removal of the lymph nodes in the groins. Very rarely, patients exposed to radiation and chemotherapy may develop leukemia or second cancers many years after exposure.

5-Fluorouracil (5FU): May cause nausea, loss of appetite, vomiting, diarrhea, skin rash, mouth and throat sores, irritation swelling and soreness of the vein where the drug is infused, temporary, reversible scalp hair loss, increased sensitivity to sunlight, skin or fingernail darkening, and depression of the bone marrow (*the blood forming organ*) which increases the risk of anemia, infection or bleeding which may be life-threatening, and which may require transfusions to correct. Occasional patients may experience chest pain or changes on the electrocardiogram which usually do not represent actual heart damage. Slurred speech, uncontrolled eye movements, loss of coordination and balance may also, rarely, occur. There have been rare instances of permanent brain damage.

Mitomycin-C: May cause temporary reduction of blood cell production, with risk of anemia, infection, or bleeding which may be life-threatening and require transfusion to correct. This may worsen with repeat courses of treatment. Possible nausea, loss of appetite, vomiting, mouth sores, fever, and mental confusion may occur. Possible kidney damage and kidney failure can occur. Infrequently, lung inflammation can happen which can cause difficulty in breathing which may be temporary, but can also result in severe, permanent lung damage.

If the drug leaks out from the vein during infusion, and infiltrates surrounding skin, swelling and local skin ulceration and pain can result which may cause permanent scarring and contracture.

Both 5FU and Mitomycin-C can cause significant, temporary weakening of the immune system which can render me more susceptible to serious infection. This is of particular concern in patients who are infected with HIV (*the virus which causes AIDS*). If I have possibly been exposed to HIV because of intravenous drug use, unprotected sexual activity, or contact with another person's bodily fluids, I should notify my doctor before participating in this clinical research.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

There are no costs incurred by participation in this research study which are not part of routine costs of tests or procedures utilized in the treatment of patients with locally extensive vulvar cancer. In the eventuality that all or a part of the costs of medical care are not covered by insurance, I may be responsible for those costs.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include surgery with or without radiation therapy either alone or with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my

doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or Legal Representative)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX III

AJCC TNM /FIGO CLASSIFICATION AND STAGE GROUPING-1988 REVISION

T- Primary Tumor

- T_x Primary tumor cannot be assessed.
T₀ No evidence of primary tumor.
T_{is} Carcinoma in situ (*preinvasive carcinoma*).
T₁ Tumor confined to the vulva and perineum 2 cm or less in greatest dimension.
T₂ Tumor confined to the vulva and perineum more than 2 cm in greatest dimension.
T₃ Tumor invades any of the following: lower urethra, vagina, or anus.
T₄ Tumor invades any of the following: bladder mucosa, upper urethral mucosa, or rectal mucosa, or is fixed to the bone.

N- Regional Lymph Nodes.

- N₀ No nodal metastases.
N₁ Unilateral regional lymph node metastasis.
N₂ Bilateral regional lymph node metastasis.

M: Distant Metastasis.
M₀ No evidence of distant metastasis.
M₁ Any distant metastasis including pelvic lymph nodes.

STAGE

- 0: T_{is}N₀M₀

I: T₁N₀M₀

II: T₂N₀M₀

III: T₃N₀M₀
T_{1,2,3}N₁M₀

IVA: T_{1,2,3}N₂M₀
T₄N_xM₀

IVB: T_xN_xM₁

(*x denotes any T or N category*)

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (*in the case of RTOG-coordinated intergroup studies*) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (*grade 4*) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- | | |
|---|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |
| - All life threatening (<i>grade 4</i>) events which may be due to agent. | As above |

- First occurrence of any toxicity (*regardless of grade*).

Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.
 **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent.

Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours
 **A written report must be sent to RTOG within working days with a copy to IDB.
 (*Grade 4 myelosuppression not reported to IDB*)

- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent.

Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
 **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

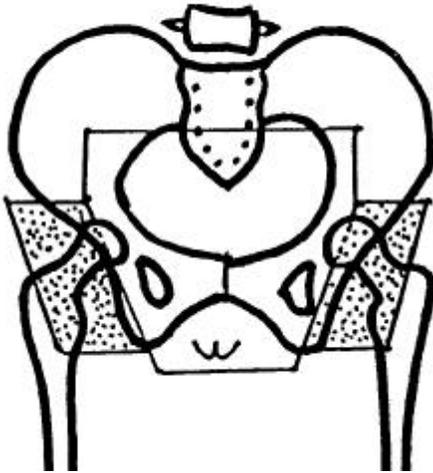
Report **in writing to RTOG Headquarters and IDB within 10 working days.

** See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form

APPENDIX VI-A

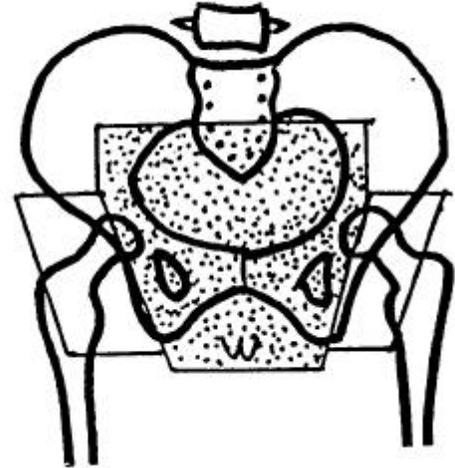
TARGET VOLUMES AND TECHNIQUES

NODE NEGATIVE PATIENTS



A. Initial treatment with photons and electrons employing a large anterior photon field and a smaller posterior photon field exclude femoral necks and lateral groin nodes.

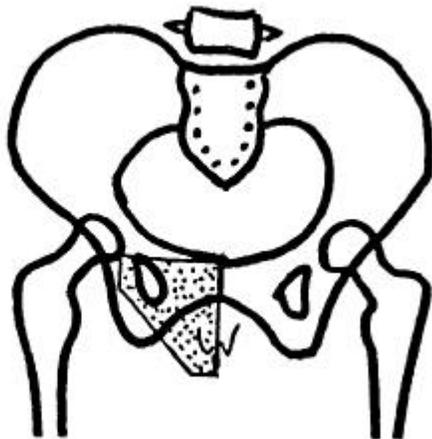
Supplementary electron fields are used to bring the total dose to the lateral groin nodes to 1.80 Gy. Stippled areas are anterior electron ports.



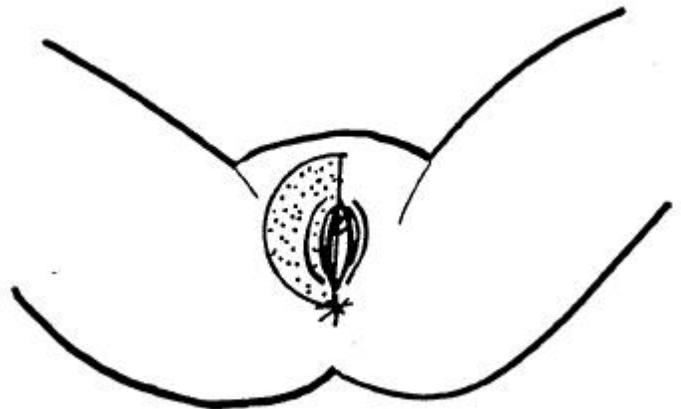
B. Initial treatment with photons only. Large anterior field includes all groin nodes.

Central to partial transmission block reduces midplane dose to .9 Gy.

Posterior photon field excludes femoral necks to deliver additional .9 Gy to midplane of volume transmission block. (*stippled volume*)



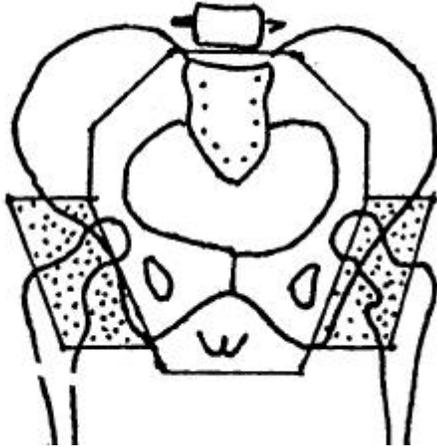
C. Sample reduced volume. For consolidative or "boost" treatment to encompass the hemi-vulva using opposed photon fields.



D. Sample reduced volume for consolidative or "boost" treatment to encompass the hemi-vulva using a perineal electron port.

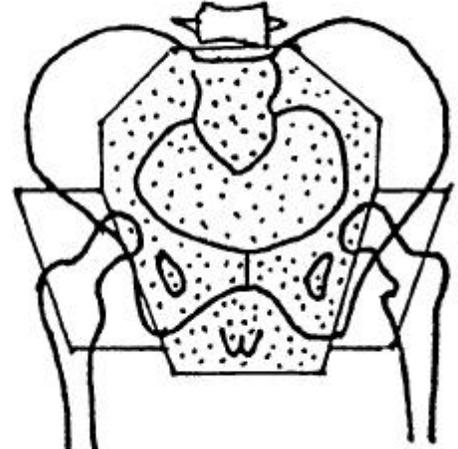
APPENDIX VI-B

**TARGET VOLUMES AND TECHNIQUES
NODE POSITIVE PATIENTS**



- A. Initial treatment with photons and electrons employing a large anterior photon field and a smaller posterior photon field exclude femoral necks and lateral groin nodes.

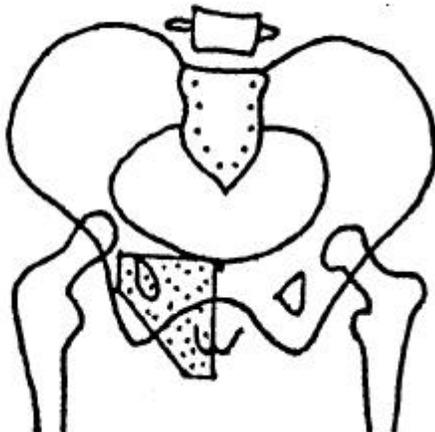
Supplementary electron fields are used to bring the total dose to the lateral groin nodes to 1.80 Gy. Stippled areas are anterior electron ports.



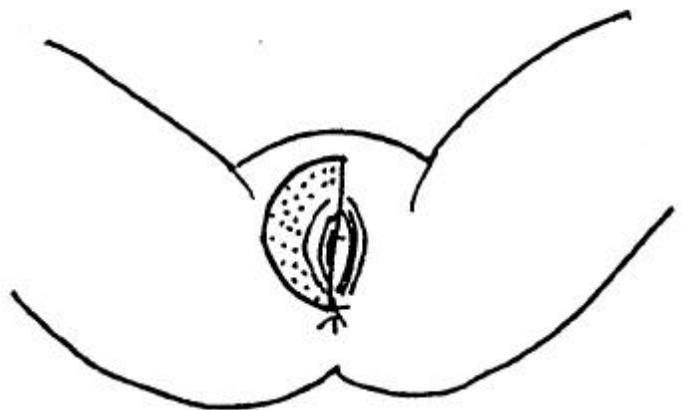
- B. Initial treatment with photons only. Large anterior field includes all groin nodes.

Central to partial transmission block reduces midplane dose to .9 Gy.

Posterior photon field excludes femoral necks to deliver additional .9 Gy to midplane of volume transmission block. (*stippled volume*)



- C. Sample reduced volume. For consolidative or "boost" treatment to encompass the hemi-vulva using opposed photon fields.



- D. Sample reduced volume for consolidative or "boost" treatment to encompass the hemi-vulva using a perineal electron port.

APPENDIX VII

GUIDELINES FOR SKIN CARE DURING CHEMORADIATION FOR CANCER OF THE VULVA.

The acute response of normal skin to radiation varies from transient, mild erythema to confluent, moist desquamation which may require weeks to heal. The severity of the acute response will be potentiated by the concurrent administration of radioenhancing chemotherapy.

Factors affecting the intensity of the skin response include volume, time, dose, fractionation, and target location. Radiation therapy for vulvar cancer cannot employ conventional, skin-sparing techniques for the treatment of what is, fundamentally, a cancer arising within specialized skin. Warmth, moisture, friction and lack of aeration will all contribute to more severe reactions on the perineum, vulva, and in the inguinal and gluteal folds. Frequent observation throughout the course of treatment and for 2-3 weeks after completion of chemoradiation is indicated to assist patients with management of, and recovery from, the acute radiation skin reaction.

PRECAUTIONS:

- 1) To cleanse the area, use lukewarm water, mild hypoallergenic soaps preferably without deodorants or perfumes, and rinse thoroughly to remove residue. Avoid friction/rubbing. Pat dry.
- 2) Avoid heavily chlorinated water or temperature extremes (*hot tubs or spas, heating pads or hot water bottles*).
- 3) Avoid tight fitting or irritating clothing. Wear loose fitting, cotton undergarments.
- 4) Minimize the use of adhesive tapes and dressings. If tape is required, use paper tape.

TREATMENT: DRY DESQUAMATION

- 1) Powder lightly with cornstarch for pruritis.
- 2) Use moisturizing lotions such as Aloe Vera, Natural Care Gel.
Apply TID/QID as needed to allow surface drying between applications, avoiding excess surface moisture.

TREATMENT: MOIST DESQUAMATION

- 1) Sitz baths in tepid water BID/TID for 15"-30" each for cleansing and gentle debridement. Avoid towel drying or rubbing. Let skin air dry if possible. Fans or a hand held hair dryer set on "fan" or "cool" may be used to dry the perineum.
- 2) Wet compresses, or very gentle use of a hand held spray shower may be used in patients unable to access a tub.
- 3) Use of Nystatin/Tetracycline/Benadryl/Hydrocortisone Elixir (*Miles' solution, "Stomatitis Elixir"*) q.4-6 H applied topically with a cotton cloth.
- 4) Application of a hydrocolloid dressing such as Vigilon can be used once or twice daily for severe reactions.
- 5) Anti-inflammatory and analgesic medication should be liberally employed on a scheduled basis to reduce discomfort.

APPENDIX VIII

PROCEDURES FOR MITOMYCIN-C EXTRAVASATION

Infiltration of a vesicant drug into tissue will cause tissue necrosis and sloughing. Healing may be slow and prolonged and result in scarring and contracture. Local management of tissue infiltration may prevent these complications. Immediate action by the nurse or physician in attendance may mitigate against severe damage. Extravasation should be suspected and treated promptly if the following signs and symptoms appear:

- 1) local pain with a burning or stinging sensation.
- 2) Redness or swelling at the injection site.
- 3) Failure to obtain free-flowing blood flashback in the I.V.

Supplies:

- 1) Hydrocortisone 100 mg/2 ml. 10 cc vial.
- 2) 1% Hydrocortisone cream.
- 3) Americaine spray.
- 4) Tuberculin size syringes.
- 5) Sterile dressing.
- 6) Paper tape.
- 7) Ice pack.

Procedure:

- 1) Remove needle from vein, and immediately apply ice pack.
- 2) Americaine spray or equivalent topical anesthetic applied to area to be injected.
- 3) Via tuberculin syringes, inject hydrocortisone both intradermally and subcutaneously in .2ml injections to completely infiltrate the area of extravasation.
- 4) Apply 1% hydrocortisone cream to the area and cover with sterile dressing
- 5) Reapply ice pack X 24 hrs.
- 6) Apply hydrocortisone cream B.I.D. until redness dissipates.

APPENDIX IX

INTRAOPERATIVE LYMPHATIC MAPPING IN ADVANCED VULVAR CANCER

Any patient with histologically confirmed metastasis to a groin node who will be undergoing superficial inguinal lymphadenectomy as part of participation in this protocol may be studied using this technique. Lymphatic mapping is not a required procedure for protocol participation, and will not be used to prescribe or alter protocol therapy. Inclusion of this technique is intended to familiarize investigators with the procedure and to potentially refine information which will be obtained from superficial groin dissections. Patients electing to participate should be asked to sign a separate consent document.

TECHNIQUE:

- 1) Patients are brought to the operating room and prepared and positioned for surgery in the routine manner.
- 2) Isosulfan Blue is injected using a 25 gauge needle into the junction of the uninvolved skin and the tumor at the point closest to the adjacent groin. If the tumor involves or crosses the midline, then the injection will be bilateral (*at the tumor/skin interface on both sides.*) In this protocol, bilateral superficial groin dissections are specified therapy for patients with histologically confirmed unilateral node metastasis.
- 3) The transit time of the dye to the groin is less than 5 minutes. Therefore, the groin dissection can proceed shortly after the injection.
- 4) The standard skin incisions are made and carried down to the level of Camper's fascia. The afferent lymphatic channels are identified and followed to one (*or more*) lymph nodes which are stained blue and are designated the sentinel nodes. The sentinel nodes are removed and sent to pathology as separate specimens.
- 5) It is anticipated that some patients in this study will have large primary tumors. Multiple injections may be performed along the broad front of the tumor. A total volume of 1 cc. of Isosulfan Blue per side is usually adequate, although more can be given without hazard.
- 6) The afferent lymphatic channels are usually seen through or just below Camper's fascia. The transit time of the dye to the lymph nodes varies but is usually less than 5 minutes. The dye may drain out of the afferent channels after 10-20 minutes rendering them invisible. The dye usually does not drain as quickly from the nodes which should remain visible for at least 30 minutes. If the sentinel node lies below the cribriform fascia, it should be removed even if not enlarged or suspicious.
- 7) The RTOG Surgical Data Form (S1) should be completed at the time of surgery.