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● *Rapid Communication*

GROIN DISSECTION VERSUS GROIN RADIATION IN CARCINOMA OF THE VULVA: A GYNECOLOGIC ONCOLOGY GROUP STUDY

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Purpose: **The objective of this study was to determine if groin radiation was superior to and less morbid than groin dissection.** ***Methods and Materials:*** **Members of the Gynecologic Oncology Group randomized 58 patients with squamous carcinoma of the vulva and nonsuspicious (N_{0-1}) inguinal nodes to receive either groin dissection or groin radiation, each in conjunction with radical vulvectomy. Radiation therapy consisted of a dose of 50 Gray given in daily 200 centiGray fractions to a depth of 3 cm below the anterior skin surface.** ***Results:*** **The study was closed prematurely when interim monitoring revealed an excessive number of groin relapses on the groin radiation regimen. Metastatic involvement of the groin nodes was projected to occur in 24% of patients based on this Group's previous experience. On the groin dissection regimen, there were 5/25 (20.0%) patients with positive groin nodes. These patients received post-operative radiation. There were five groin relapses among the 27 (18.5%) patients on the groin radiation regimen and none on the groin dissection regimen. The groin dissection regimen had significantly better progression-free interval ($p = 0.03$) and survival ($p = 0.04$).** ***Conclusion:*** **Radiation of the intact groins as given in this study is significantly inferior to groin dissection in patients with squamous carcinoma of the vulva and N_{0-1} nodes.**

Carcinoma of the vulva, Groin radiation, Groin dissection.

INTRODUCTION

Radical vulvectomy with bilateral groin (inguinal and femoral) lymph node dissection is the standard therapy for carcinoma of the vulva (3, 10, 12, 14, 18, 19). This operation is curative for a majority of patients with survival rates reported to approximate 67–76% (3, 12, 18, 19). The cure rates approach 90–95% for those patients who have resectable primary tumors and who are without evidence of metastatic disease in nodes (3, 10, 12, 18, 19, 21). Local control on the vulva has been excellent with this operation. Durable local control has been achieved in 91.9% of 588 patients in the Gynecologic Oncology Group (GOG) experience (10).

The frequency of positive groin nodes has ranged from 21% to 34.5% (10, 15, 19). Patients with metastatic disease in groin nodes have a poorer prognosis (3, 4, 10, 11, 18, 19). Homesley *et al.* (9) and Podratz and co-workers (9)

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found a significant decrease in survival as the number of positive nodes increased from one to two. Curry *et al.* (4) found that patients with three or fewer involved nodes had a reasonably good prognosis, but patients with four or more nodes all succumbed to their disease. Overall rates of survival correlate with the proportion of node-positive patients.

Clinical negative-node status predicted pathologic negative nodes in 76.3% of patients with N_{0-1} nodes (10). In Morley's experience (18), 19.5% of patients with N_{0-1} nodes had clinically occult metastases. Downstaging of N_2 nodes has been as common or more common than upstaging (10, 18, 19). Multiple other factors correlate with positive nodes. In addition to clinical node status, Boyce *et al.* (2) found a correlation with depth of invasion and pattern of invasion. Multi-variate analysis of the GOG data has shown that clinical node-status, GOG grade, capillary-lymphatic space involvement, tumor thickness, and age were independent risk factors for positive groin nodes (10). Clinical status has been a useful though inexact reflection of both the number of positive nodes and bilaterality (9). The majority of patients with positive nodes (62.5%) had only one or two nodes involved (10). Patients with clinical N_2 nodes were more likely to have bilateral involvement.

Radical operation is associated with morbidity associated with wound healing and lymphedema. In GOG Protocol #36, (10) 27% of patients suffered some degree of chronic lymphedema, and 49% experienced wound breakdown. Podratz and co-workers (19) observed impairment of primary wound healing in 85% of patients and lymphedema in 69%. Morley described edema as "frequent" and reported a 50% wound complication rate (18). Cavanagh *et al.* (3) reported a 54% rate of wound complications. The operative mortality has ranged from 2.2% to 5.8% (12, 19).

These complications have been associated primarily with the groin dissection. Patients who undergo vulvectomy without groin dissection are known to have fewer complications and shorter hospitalizations (18). The high rate of complications becomes more difficult to accept when one notes that 70–80% of patients have negative nodes. Radiation of intact nodal groups at risk to harbor occult metastases has been effective in squamous tumors of other sites. GOG protocol #37 (9) compared pelvic and groin radiation to pelvic lymphadenectomy in post-operative patients who were found to have metastatic disease in inguinal or femoral nodes at groin dissection. There was a significantly superior progression-free interval (70% vs 51%, $p = 0.004$) and survival (79% vs 54%, $p = 0.0005$) at 2 years for the radiation regimen, as well as improved control in the groin (94.9% vs 76.4%).

Adjuvant radiation may have a role to play in decreasing the radicality of the primary treatment. There is evidence to support elective irradiation of intact groin nodes. Frischbier and Thomsen (6) treated 118 patients with electron beam and achieved a 70% survival among patients with N_{0-1} nodes. No information was given on sites of failure or control in the groin, however. There was an 8% overall severe complication rate in the groin, though this may have been related to the dose of 45–54 Gy given in 300 Cgy daily fractions or to the high rate of N_{2-3} patients in the series. Henderson *et al.*, (8) following up on a previous report by Daly, (5) treated 91 patients with tumors of a variety of primary sites including vulva, cervix, vagina, and penis. There were no failures in the radiation field in the groin, but 2 of 49 evaluable patients failed in the groin outside of the treatment field even though their primary lesion had been controlled. One patient suffered bilateral femoral neck fractures. More recently, Kucera and Weghaupt (14) have reported a 67% absolute survival for 72 patients with N_{0-1} groin nodes treated with operation to the vulva and irradiation to the groins.

Encouraged by the report of the superiority of post-operative irradiation in positive groin node patients (9) and discouraged by the morbidity of groin dissection, the GOG undertook a randomized comparison of groin radiation versus groin dissection to compare efficacy and morbidity of the two treatment approaches, and to monitor patterns of recurrence and survival of patients treated with groin radiation in lieu of groin dissection.

METHODS AND MATERIALS

Eligibility

Only patients with a primary, previously untreated, squamous cell carcinoma of the vulva were eligible for this study. A radical vulvectomy had to suffice to remove the primary lesion (T_{1-3} FIGO, 1971). Patients with T_1 tumors were eligible only if there was capillary-lymphatic space involvement or if there was >5 mm of invasion. Lymph nodes, if palpable, must not have been suspicious (N_{0-1}). Needle aspiration cytology was required if there was any concern over node status. Patients with distant metastasis (M_1) were not eligible. All patients had a complete history and physical examination, blood count, serum electrolytes, renal function studies, chest roentgenogram, and cardiogram. Computed tomography of the pelvis was recommended. Patients who were medically unsuited for operation were ineligible as were patients who had received any prior radiation therapy or chemotherapy. Also ineligible were patients who had any prior malignancy other than nonmelanoma skin cancer of a site other than the vulva. All patients had given informed consent to study in accordance with local IRB guidelines and with the Treaty of Helsinki.

Treatment plan

Eligible patients were randomized to undergo radical vulvectomy and bilateral inguinal-femoral lymphadenectomy or radical vulvectomy followed by bilateral groin radiation.

Surgical procedure

All patients underwent a radical vulvectomy as previously described (10). A margin of normal skin around the lesion was prescribed. In most cases the wound could be closed primarily, but local flaps and other closure or coverage techniques were left to the discretion of the operating surgeon. Those patients with Stage I disease ($T_1N_0M_0$, $T_1N_{0-1}M_0$) were permitted to undergo modified radical hemivulvectomy if this operation encompassed the primary lesion with an adequate margin.

For those patients randomized to the control regimen, bilateral inguinal-femoral lymphadenectomy was also performed. Suction drains were used almost universally. Patients found to have microscopic disease in nodes received radiation therapy to the ipsilateral groin and hemipelvis (9). All records, including the operative report, were reviewed by the Gynecologic Oncology Committee of the GOG to assure that eligibility criteria had been met and that the operative procedure was in concordance with GOG guidelines.

Radiotherapy procedures

Patients randomized to the groin radiation regimen commenced their treatment within 4 weeks of operation. The groins were treated daily to a dose of 50 Gy over 5 weeks (200 cGy/day). Dose was calculated at 3 cm below the anterior skin surface. Photon beam energy of at least 4–6 MeV was required, and it was recommended that 50% of the prescribed dose be given with 12–13 MeV electrons to reduce the dose to the femoral heads.

Bilateral groin radiation had the following borders (Fig. 1): superior, the anterior superior iliac spine (ASIS); superomedial, 2 cm above a line from the ASIS to the pubic tubercle (PT); lateral, dropping vertically from the ASIS; inferolateral, 8 cm below the line from the ASIS to the PT; medial, 2 cm lateral to the midline but no further lateral than the medial border of the obturator foramen. The primary site and the pelvic nodes were not treated.

Patients randomized to the groin dissection arm who were found to have metastatic carcinoma in the resected nodes received post-operative radiation therapy to the ipsilateral groin and hemipelvis (8). A total dose of 50 Gy was administered through anterior portals to the groin and through anterior and posterior portals to the iliac nodes.

Daily radiation treatment records and calculations as well as port films were reviewed by the study co-chairman (MV) as well as the Radiation Oncology Committee of the GOG. Dosimetry control for this clinical trial was supervised by the Radiologic Physics Center (RPC) under the sponsorship of the American Association of Physicists in Medicine.

Pathology procedures

The excised tissues were reviewed at the GOG member institutions prior to study entry. Representative stained slides demonstrating the deepest penetration of the tumor and the institution's pathology report were submitted for review. The submitted report included a description of the anatomic location of the lesion, the size of the lesion, histologic grade, and the number of lymph nodes examined. These slides and forms were reviewed by the Pathology Committee of the GOG in all cases to confirm diagnosis, cell type, and grade.

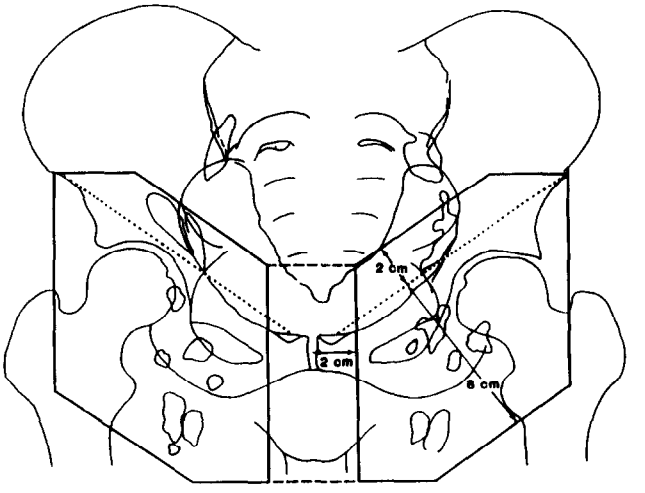

Fig. 1. Radiation treatment fields.

Data analysis

Records and follow-up data were submitted by member institutions to the GOG offices for compilation and review. Adverse effects were reported according to standardized GOG criteria (1). Any severe or life-threatening adverse effects were reported immediately to the GOG Group Chairman and to the study chairman. In addition to the Committee review noted above, each patient record was reviewed by the study chairman (FBS) for suitability, accuracy and consistency.

Randomization was carried out by a block arrangement balanced within and across institutions and for T/N substage classification. The major parameters of response were survival, progression-free interval, and site of recurrence. Adverse effects including wound complications, lymphedema, and length of hospitalization were tabulated. The accrual goal was based on accrual of 300 patients with follow-up until 105 recurrences were observed in the groin dissection group. This number of recurrences would produce a power of 0.79 when the probability of a Type I error was at 0.05 (one-sided test).

The study was placed on accrual hold in April, 1990 when a difference between the two study arms was observed. The study was closed 6 months later when additional follow-up confirmed these differences. It should be pointed out that periodic monitoring of differences invalidates the meaning of the p value associated with the classical hypothesis test. The decision to close this study prematurely on the basis of interim monitoring was made only after careful deliberation.

Recurrence-free interval was defined as the time from study entry to physical or radiological evidence of disease

recurrence or date last seen. Survival was defined as the time from study entry to death or date last seen. All life-tables and rates were computed using the product-limit estimate by Kaplan and Meier (13). The log-rank test (16) was used for testing differences in recurrence-free interval and survival among patient groups. Difference in age, days hospitalized and quetelet index between regimens were tested using Krushel-Wallis test. All other factors were tested using the Pearson's chi-squared test (20).

RESULTS

Between August, 1986 and April, 1990, 21 GOG member institutions entered 58 patients on study. There were six (10.3%) patients declared ineligible on review. Five patients had incorrect stage and one had wrong primary site. All 52 eligible patients were evaluable. This report is based on the findings and outcomes of these 52 eligible patients. At this point in follow-up, 54% of patients have been followed for at least 3 years or have recurred.

The median patient age was 64 years, first and third quartiles (Q1, Q3) 51.5 and 75.5, respectively. Clinical patient characteristics are tabulated on Table 1. Pathologic characteristics are listed on Table 2. There are no imbalances of risk factors between the regimens, though the groin radiation patients were slightly younger ($p = 0.11$) and had better performance status ($p = 0.11$).

Table 1. Patient characteristics

Risk factors	# Cases (%) Groin dissection	Groin radiation
Age:		
31–40	1 (4.0)	3 (11.1)
41–50	1 (4.0)	6 (22.2)
51–60	5 (20.0)	4 (14.8)
61–70	7 (28.0)	5 (18.5)
71–80	5 (20.0)	6 (22.2)
81–90	6 (24.0)	3 (11.1)
Race:		
White	21 (84.0)	20 (74.1)
Non-white	4 (16.0)	7 (25.9)
GOG performance grade:		
0	10 (40.0)	19 (70.4)
1	11 (44.0)	7 (25.9)
2	2 (8.0)	1 (3.7)
3	2 (8.0)	0 (0.0)
Clinical node status:		
Not palpable (N_0)	20 (80.0)	20 (74.1)
Palpable but normal (N_1)	5 (20.0)	7 (25.9)
Quetelet index $\frac{\text{wt in kg}}{(\text{ht in m})^2}$*		
≤ 22	4 (16.0)	4 (15.4)
22.1–24	3 (12.0)	4 (15.4)
24.1–28	7 (28.0)	3 (11.5)
> 28	11 (44.0)	15 (57.7)

* One patient—height unknown.

Table 2. Pathologic characteristics

Pathologic risk factors	# Cases (%) Groin dissection	Groin radiation
Clinical tumor size (cm):		
≤ 2.0	2 (8.0)	3 (11.1)
2.1–4.0	18 (72.0)	19 (70.4)
≥ 4.1	5 (20.0)	5 (18.5)
Tumor grade:		
Well differentiated	8 (32.0)	8 (29.6)
Moderately differentiated	14 (56.0)	14 (51.9)
Poorly differentiated	3 (12.0)	5 (18.5)
Location of tumor		
Labia	14 (56.0)	16 (59.3)
Clitoris	6 (24.0)	5 (18.5)
Perineum	3 (12.0)	6 (22.2)
Other	2 (8.0)	0 (0.0)

There were three patients randomized to receive groin radiation who declined to complete radiation therapy. All patients randomized to the groin dissection regimen were operated upon.

Acute complications were as expected. There were 22 episodes of Grade 3 or 4 toxicity among 14 of the patients who underwent radical vulvectomy and groin dissection. The most prevalent event was Grade 3 cutaneous toxicity, 12 wound disruptions. There were five severe or life-threatening cardiovascular complications (4 Grade 3, 1 Grade 4). Among the 24 patients who underwent radical vulvectomy and completed groin radiation there were ten episodes of Grade 3 toxicity; there were no Grade 4 adverse effects in this group. Seven of the ten episodes represented cutaneous toxicity.

Seven of the 25 patients on the groin dissection regimen had mild or moderate lymphedema. There were no other chronic adverse effects reported. None of the patients on the groin radiation regimen suffered femoral neck fracture.

The median post-operative stay was 13 days (Q1:8, Q3: 20). The patients treated with groin radiation had substantially shorter hospitalizations than those who underwent groin operation ($p = 0.0001$ Table 3).

There was one treatment-related death. A 73 year old patient treated on the groin dissection regimen was discharged from the hospital on the 18th post-operative day. Nine days later she suffered a massive pulmonary embolus, confirmed by autopsy. This represents the Grade

Table 3. Hospital stay

Hospital stay	# Cases (%) Groin dissection	Groin radiation
≤ 7 days	2 (8.0)	10 (38.5)
8–12 days	3 (12.0)	10 (38.5)
≥ 13 days	20 (80.0)	6 (23.1)

One patient did not have protocol surgery.

Table 4. Recurrences and deaths

Recurrences/deaths	# Cases (%)	
	Groin dissection	Groin radiation
Recurrence:		
Vulvar	1 (4.0)	1 (3.7)
Groin	0 (0.0)	5 (18.5)
Distant	1 (4.0)	2 (7.4)
None	23 (92.0)	19 (70.4)
Deaths:		
Treatment	1 (4.0)	0 (0.0)
Intercurrent	1 (4.0)	2 (7.4)
Disease	1 (4.0)	8 (29.6)
Alive	22 (88.0)	17 (63.0)

4 cardiovascular adverse event. Two patients on the groin radiation regimen died of intercurrent disease; one of a primary lung cancer and the other of complications of therapy for a primary colon cancer. One patient on the groin dissection regimen died of myocardial infarction 2 years after operation.

On the groin dissection regimen, there were 5/25 (20%) patients with positive groin nodes. These patients had the following number of positive groin nodes: 1, 1, 1, 3, and 4. In total there were 10 (19.2%) patients with recurrence of their vulvar carcinoma, two on the vulva, five in the groin, and three at regional/distant sites (i.e., beyond the vulva or groins) (Table 4). All of the five patients who recurred in the groin had had complete radiation. All of these groin recurrences were within the treatment field. Computed tomography was performed and reported to the GOG offices on three eligible patients on the groin dissection regimen including one patient who was found to have positive groin nodes. Computed tomography (CT) was performed and reported to the GOG offices on eight patients on the groin radiation regimen including one of the patients who developed a recurrence in the groin. It should be noted that as this study was not required, additional patients may have had CT which was not reported.

A careful review of the details of treatment for these five patients did not reveal any violation of protocol guidelines or deviation with regard to total dose, treatment duration, or RPC dosimetry (Table 5). All patients whose disease recurred in the groin have died of their disease. Progression-free interval (Fig. 2), observed survival (Fig. 3), and relative survival (intercurrent deaths censored) (Fig. 4) are compared for the study population and for the controls. The significance level of progression-free interval, observed survival, and relative survival are $p = 0.033$, $p = 0.035$, and $p = 0.042$, respectively.

DISCUSSION

Incorporation of radical bilateral operation on the vulva and groins into the primary treatment plan for carcinoma of the vulva brought about a notable improvement in outcomes for patients with this disease. Variations of radical vulvectomy and bilateral groin dissection are well-established as the standard treatment for vulvar cancer (3, 10, 12, 15, 18, 19). This operation produces a high rate of durable local control on the vulva. Groin node status is the most significant prognostic factor for survival (10).

Though well-tolerated by an older population, the morbidity of the procedure is considerable. Acute wound complications and late lymphedema are common, and operative mortality is not a rare event. For patients who have small superficial tumors, morbidity can be reduced by modifying the extent of the operation (21). This approach may increase the risk of recurrence. Modified operation is not an acceptable option for patients with more extensive disease.

The GOG recognized that (a) the morbidity of radical operation is largely associated with bilateral inguinal-femoral lymphadenectomy, (b) only 24% of patients with N_{0-1} groin nodes have groin metastases, most of which are microscopic deposits in one or two lymph nodes, and (c) post-operative radiation is superior to pelvic node dissection in the treatment of patients with metastatic disease in groin nodes. For these reasons, it appeared that a randomized comparison of groin radiation versus groin dissection, each in conjunction with radical vulvectomy, would have the potential to improve outcome and quality

Table 5. Patients with groin failures

No.	Stage/ lesion size	Tumor grade	Quetelet index	Photon energy/dose	Electron energy/dose	Total dose/ RT duration	Time from study entry to recurrence
1	T_2N_0/ 2.1 × 2.0 cm	2	25	6 MeV 2600 cGy	12 MeV 2400 cGy	5000 cGy/ 34 days	2 months
2	T_2N_0/ 2.3 × 1.9 cm	3	33	6 MeV 2475 cGy	13 MeV 2515 cGy	4989 cGy/ 42 days	17 months
3	T_2N_0/ 5.0 × 4.0 cm	3	24	6 MeV 5109 cGy	None	5109 cGy/ 42 days	7 months
4	T_2N_0/ 4.0 × 2.0 cm	2	28	10 MeV 4845 cGy	None	4845 cGy/ 31 days	7 months
5	T_2N_0/ 3.0 × 2.5 cm	3	38	4 MeV 2600 cGy	12 MeV 2400 cGy	5000 cGy/ 35 days	6 months

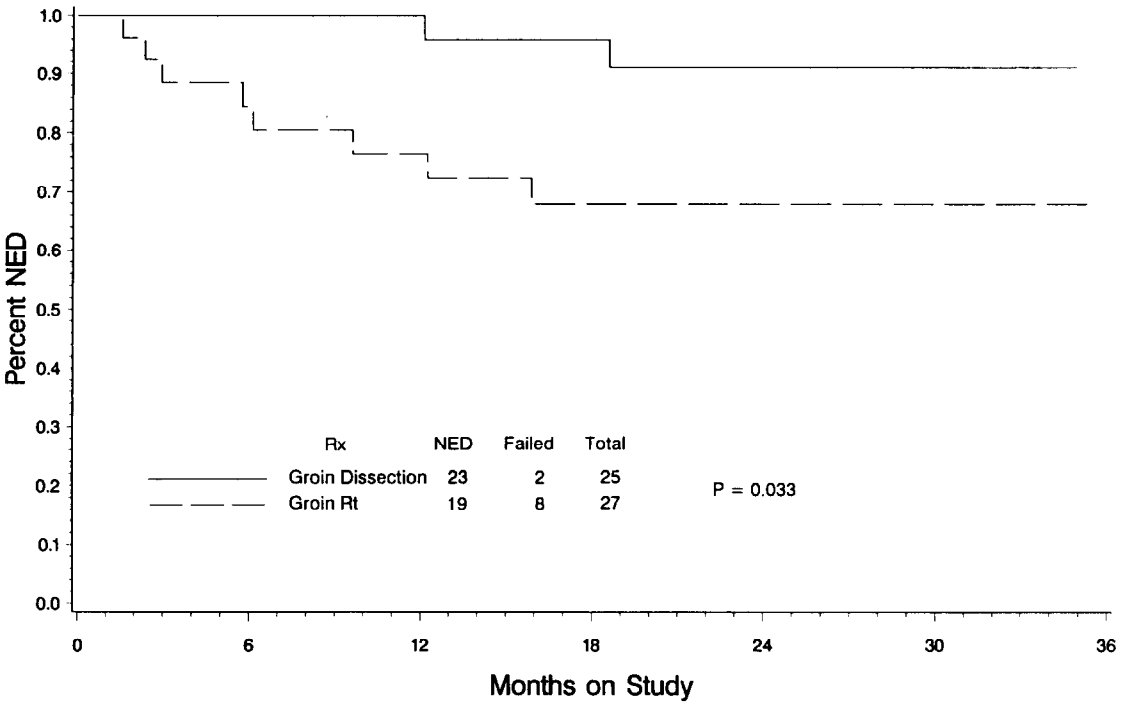

Fig. 2. Progression-free interval by treatment.

of life for these patients. The number of patients with groin node metastasis observed on the groin dissection regimen of this study was comparable to the number expected (24%) based on previous GOG experience (10). It would appear that groin radiation failed to control any patient's groin metastasis.

Three-fourths of the patients were expected to have negative groin nodes. Patients were randomized prior to any therapy. In order to reduce the likelihood that a patient with macroscopic groin disease would be entered on study, CT was recommended as a pre-entry evaluation. Risk factors for aggressive behavior and for probability of nodal metastasis were balanced between the two randomization arms. We consider it unlikely that the group of patients randomized to receive groin radiation included more individuals with node metastases or that these pa-

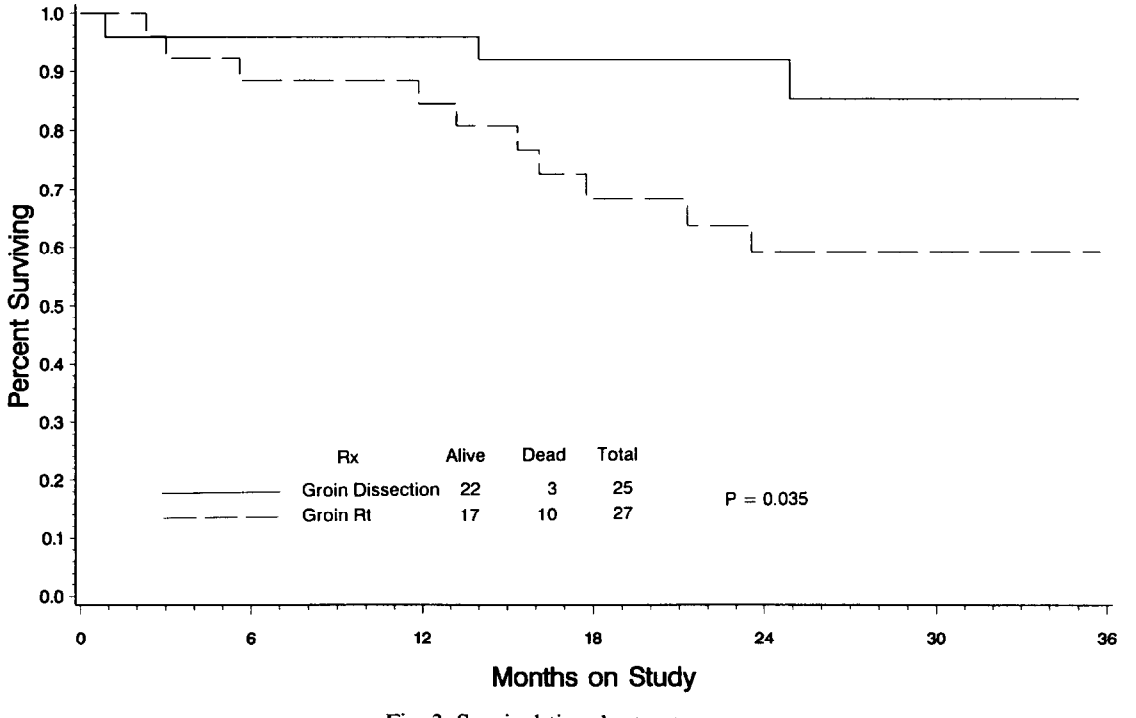

Fig. 3. Survival time by treatment.

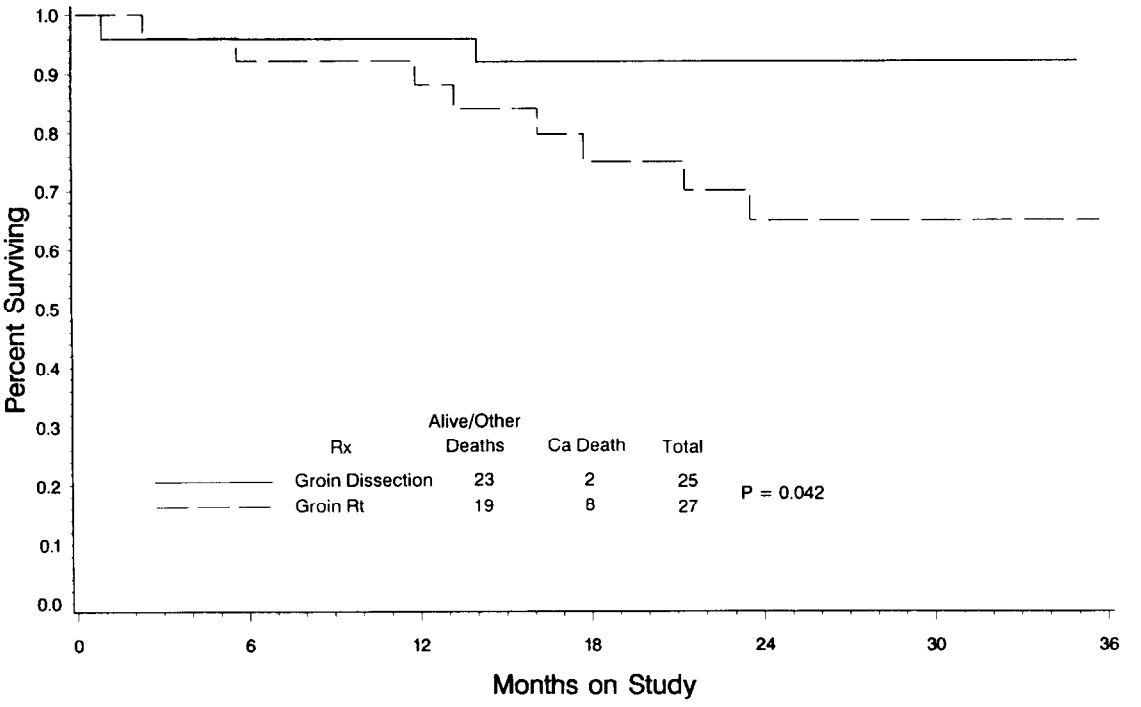

Fig. 4. Relative survival time by treatment.

tients had biologically more aggressive tumors. The number of nodes involved and the nodal volume would be expected to be similar on both regimens.

We estimated that 50 Gy could sterilize microscopic squamous carcinoma in more than 90% of patients. Marks (17) has pointed out that required dose depends on multiple factors. In designing this study the probability of disease being present and the number of sites were determined from the previous surgico-pathologic study of 588 patients (10). Eligibility was limited to squamous cell carcinoma to minimize variation in sensitivity. Desired control rate was determined by the statistical design.

Interim monitoring in early 1990 revealed five patients with groin failure among the 27 patients on the groin radiation regimen compared to five patients found to have positive nodes on the groin dissection regimen, none of whom had suffered groin relapse. At that time the study was closed to new patient entry (accrual hold). Sites of failure, survival, and progression-free survival were monitored for differences between the study populations as randomized (Figs. 2 and 3).

It is not clear why radiation failed to control disease in the groin in these patients. Two possible explanations should be considered related to volume and dose, respectively.

Not all subclinical disease should be thought of as microscopic. Clinical evaluation of the groin is difficult, but we presume that the frequency and volume of groin metastasis was comparable between the two treatment groups. This presumption is supported by our previous experience (9). The dose prescribed in this study would be expected to control microscopic post-operative disease. Occult nodal disease in the intact groin may be underestimated, in which case the prescribed dose would have been inadequate. Two of the five patients on the groin dissection arm had centimeter volume disease in the resected nodes.

Nodal disease could have been underdosed because of its location. Dose was prescribed 3 cm below the anterior skin surface. Nodes deeper than 4 cm would have been underdosed if 50% of the prescribed dose was given with 12–13 MeV electrons. The dose to depth curve is quite steep with this prescription.

As expected, the probability of salvage of patients with relapse in the groin is exceedingly low. There were no survivors in the experiences reported by Cavanagh, (3) Hacker, (7) or Hopkins (11). With short follow-up, 4 of 9 patients on the GOG study of early-stage disease are still alive (21). These patients relapsed in a groin that had previously been subjected to a superficial dissection only. Three of the four survivors in that study were treated with reoperation and radiation.

Groin dissection provides prognostic information with therapeutic implications. Those five patients on the groin dissection regimen who were found to have positive groin nodes also received post-operative irradiation. None have suffered relapse in the groin. Follow-up is short, however, and additional deaths can be expected among these control patients based on previous experience.

The patients who were randomized to receive groin radiation with radical vulvectomy had shorter hospital stays and fewer treatment complications. The excess number of relapses and deaths in this population clearly outweigh the consideration of decreased morbidity. Groin

dissection is significantly superior to groin radiation therapy with regard to survival and progression-free interval. We do not believe that this report negates the value of post-operative radiation, previously reported (8). Radical vulvectomy and inguinal-femoral lymphadenectomy followed by radiation therapy for patients with metastases in groin nodes will continue to be the standard therapy for future GOG studies for this group of patients.

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