The role of radiation therapy in the management of invasive squamous cell carcinoma of the vulva

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INTRODUCTION Radical vulvectomy with bilateral groin lymphadenectomy has been regarded as standard treatment for resectable invasive squamous vulvar carcinoma. There is no advantage in routinely performing pelvic node dissection (1). Current management of pelvic lymph nodes is guided by prognostic factors and includes dissection of any enlarged nodes followed by postoperative groin and pelvic radiotherapy. The place of pelvic lymphadenectomy in high-risk patients of developing pelvic recurrences has yet to be determined. En bloc radical vulvectomy and bilateral inguinofemoral node dissection has been superseded by the triple incision technique (radical vulvectomy with separate groin incisions) (2), practically in all patients with primary tumor confined to the vulva who do not have enlarged groin nodes. The triple incision technique has been demonstrated to be as effective as the en bloc procedure and has been associate with significantly less morbidity (3). For small primary tumor first modified radical vulvectomy, later radical local excision has been advocated with comparable local control and survival rates. In fact, the surgical margins adjacent to the tumor are the same with radical vulvectomy and radical local excision.

Some of the problems associated with the basic surgical strategy include:

- Radical vulvectomy is a mutilating procedure which is not infrequently associated with devastating psychosocial consequences and compromised sexual function in younger women.
- Mild to severe complications frequently occur, some of them, especially leg edema following groin node dissection are severely debilitating.
- Women with vulvar cancer are at high surgical risk due to advanced age and associated medical conditions such as obesity, hypertension, diabetes, cardiovascular diseases, etc.

Over the past 20 years, great strides have been made to overcome some of the major concerns associated with the traditional management of invasive squamous carcinoma of the vulva. These include less radical surgical excision of the primary tumor in early cases, replacing exenterative treatment with organ-sparing procedures in advanced stages, recognition the need of individualized treatment, confirm the validity of the sentinel node concept, introduction of a safe a simple method of intraoperative lymphatic mapping (4), etc. This later approach is a potentially valuable intraoperative tool for assuring removal of the sentinel node and thereby increasing the efficacy and defining the extent of groin dissection and whereby reducing the incidence of lymphedeme.

In the past, the role of irradiation in the primary treatment of vulvar cancer was limited, mainly, because the results were less favorable than those with surgery, and perhaps, because of the high incidence of severe complications and poor tolerance of radiation therapy by the vulvar tissue. However, several recent reports suggest that with high-energy equipment, radiation therapy can be performed without producing radiation necrosis and significant severe complications. The advantages of radiotherapy in the management of squamous cell carcinoma of the vulva have been increasingly appreciated and the indications for are evolving. The possible sites of irradiation include 1. vulva with the adjacent tissue/organs, 2. groin lymph nodes and 3. pelvic lymph nodes.

RADIOSENSITIVITY OF SQUAMOUS CELL CARCINOMA OF THE VULVA Sufficient data have accumulated suggesting that irradiation could eradicate or at least cause major regression of vulvar cancer in a significant proportion of patients (5-10). Like squamous carcinomas of the anal canal, vulvar cancer appears to regress rapidly during radiation therapy. Complete remission may occur before the treatment is completed but, as a rule, within 4 to 6 weeks of completion of irradiation. Thus, vulvar cancer is radiosensitive; probably as sensitive as squamous cancer of the skin and more sensitive than that of the cervix or vagina. However, necrotic tumors and atrophic epithelial structures often fail to respond satisfactorily to radiation therapy (8).

CAN RADIATION THERAPY ERADICATE INGUINAL LYMPH NODE METASTASES? Clinical evidence suggests that microscopic groin

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node metastases may adequately be treated with radiation therapy (7, 11-15). However, macroscopic inguinal node metastasis usually requires surgical excision prior to irradiation. Grossly positive nodes are unlikely to be cured by irradiation alone (11, 16).

RADICAL VULVECTOMY WITH ELECTIVE INGUINAL RADIATION

Elective groin radiation, i.e. radiation therapy to the groin without inguinofemoral lymphadenectomy combined with the surgical management of the primary tumor has been advocated. Elective groin node irradiation may be given simultaneously or after the surgical treatment of the primary tumor. The largest series of 607 patients with various stages of vulvar cancer treated with elective groin radiation has been reported on from Vienna (17-18). Nodes larger than 2 cm were excised. The cure rate was comparable with that of groin node dissection irrespective of the clinical nodal status. In this series the pelvic nodes were not irradiated. *Schultz et al.* (19) reported a single regional failure of 38 patients with elective groin radiation versus 5 regional failures out of 35 nonirradiated patients. *Henderson et al.* (20) studied 41 patients (31 St I, 6 St II, 4 St III) with no palpable nodes treated with elective groin radiotherapy. Only one patient experienced regional recurrence that was outside the irradiated area. The advantages of elective ilioinguinal node irradiation have also been demonstrated in other series (12, 17, 21-23). Recently, the GOG (24) reported the results of a phase III study. Patients with invasive vulvar cancer with no clinically suspect groin nodes were allocated to either undergo inguinofemoral node dissection followed by postoperative groin radiation for patients with positive nodes or receive primary groin irradiation of 50 Gy to a depth of 3 cm below the skin surface. Enlarged nodes were cytologically evaluated and those with positive findings were excluded. The study was closed prematurely because of the high incidence of groin recurrences in the elective radiation arm of the study. This finding is against to give primary groin radiation. However, this study has been criticized (25). The failure in the radiation arm might be attributable to methodological error because the deepest groin nodes measured on CT scans were to be located deeper than 3 cm (around 5 cm) below the skin surface in approximately half of the patients, consequently they did not receive adequate radiation dose. This criticism along with the experience accumulated in the literature suggests that elective groin radiation is an alternative to full inguinofemoral lymphadenectomy (26). Lower incidence of acute and delayed morbidity including leg edema after elective groin radiotherapy has been reported, and this is the major advantage of this approach as compared to the traditional surgical management of the groin nodes with or without postoperative groin radiation.

PREOPERATIVE RADIATION OF THE PRIMARY TUMOR

EARLY STAGES Currently, we do not have reports suggesting that preoperative radiation of T1 or T2 tumors is beneficial unless the tumor is located on either the perineum or clitoris. Surgery alone is probably an adequate treatment for such lesions. Stage I and II squamous cell carcinoma of the vulva encroaches on either the perineum or clitoris may well be treated with preoperative irradiation or chemoradiotherapy to reduce tumor size and thereby permitting tissue sparing surgical excision.

LOCALLY ADVANCED LESIONS Locally advanced vulvar cancer has a varied presentation and may be defined as tumors involving the lower urethra, vagina, anus (T3 primary tumor) or bladder mucosa, rectal mucosa, upper urethra, pelvic bone (T4 primary tumor). *Hoffman et al.* (27) consider vulvar cancer to be locally advanced when the tumor cannot be locally managed by a radical vulvar resection.

Primary surgical management of locally advanced vulvar cancer with the aim of adequate surgical clearance requires radical, mostly exenterative intervention with additional groin node with or without pelvic node dissection. This may include resection of the pubic bone in selected cases (28). *Radical vulvectomy* for T3 tumors has been reported to carry a high risk of local recurrence (29). Depending on the tumor location, with *anovulvectomy* or *radical vulvectomy and partial resection of the rectum with reconstruction or, even preservation of the anal sphincter* the primary locally advanced tumor can adequately be managed (30-31) *Pelvic exenteration* (anterior, posterior or total), as primary therapy, is rarely indicated. It is a viable option when organ-preserving treatment, i.e., preoperative radiation with or without chemotherapy has failed. It may also be indicated for large invasive primary vulvar cancer in patient not eligible for organ preservation (32). The major prognostic factor in terms of recurrence following pelvic exenteration is the presence of lymph node metastases (27, 33-34). Thus, careful regional node dissection prior to exenteration is required. Locally advanced disease with node involvement apparently cannot be controlled by pelvic exenteration alone. In the absence of nodal involvement, 50-75% 5-year survival rate can be expected (32-34). Therefore, according to *Homesley et al.* (35) it is not reasonable to utilize exenterative surgery in patients with locally advanced primary carcinoma of the vulva who have more than one or perhaps two microscopic positive inguino-femoral nodes. Other prognostic factors for survival include tumor size and clear margins. Ultraradical surgical approaches are mutilating often with compromised organ function, psychologic morbidity and significant risk of medical complications (36-37). Age per se is not a contraindication, pelvic exenteration can safely performed in elderly women (32, 38).

Preoperative irradiation (external, interstitial) with or without chemotherapy has been utilized to bring about tumor shrinkage, thus permitting less radical surgery with possible sparing bladder and/or rectal function (16, 39-43). It has been assumed and was one of the reasons to administer radiation therapy prior to surgery, that preoperative external radiation would control any microscopic disease in the uninvolved vulva to allow conservative surgical excision. However, there is no evidence that the normal-looking vulva harbors microscopic tumor deposits.

Boronow (40) was the first to suggest preoperative irradiation with intracavitary radium with or without external beam irradiation in women with locally advanced vulvar cancer to eliminate internal tumor followed by surgical excision of the external genital disease. Subsequently, *Hacker et al.* (16) reported on 8 patients treated with teletherapy and there was no residual disease in the specimens of 4 patients. Long-term survival has been achieved in two patients with tumors fixed to the pelvic bones. With further experience external beam irradiation with use of brachytherapy in selected cases only has been recommended. Although most reported series have been based on small numbers, tumor regression following 40-50 Gy external beam irradiation apparently is not infrequent with complete response in half of the patients depending on, the stage, the size of the tumor and the radiation dose delivered (16, 41, 44). Exenterative surgery or removal of the entire vulva was not necessary in patients with complete or nearly complete disappearance of all gross disease. The prognosis of complete responders as compared to partial responder is significantly better. The outcome of non-responders is generally poor. The width of the tumor-free resection margins appears to be important in terms of local control. Subclinical residual disease has been found in the surgical specimen in a substantial number of patients with complete disappearance of all gross tumor following radiation therapy, and excision of the tumor bed has been advocated. The overall results of combined treatment of locally advanced disease show that the cure rate is comparable or even better than that of radical surgery, and the primary mortality and treatment morbidity are significantly decreased. Bladder and/or rectal function may be preserved in approximately 70% of patients with T3 or T4 lesions. Sparing of vulvar tissue may also be possible in some instances.

THE ROLE OF POSTOPERATIVE VULVAR AND GROIN RADIATION THERAPY

POSTOPERATIVE IRRADIATION OF THE VULVA No prospective randomized study has been reported on the value of adjunctive vulvar radiation therapy after radical vulvectomy. Some reports suggest that radiation treatment may have value in controlling vulvar lesion (45). Whether it is true for patients with properly excised vulvar tumor has yet to be determined. At present, surgery alone is the preferred treatment in such cases. Local vulvar recurrence is not uncommon when the surgical margin of the excised vulvar tumor is not adequate, and therefore postoperative vulvar radiation appears to be indicated in this setting. However, surgical margin as a prognostic factor has not been subjected in most studies. Consequently, the beneficial effect of the adjuvant vulvar radiation therapy is not clear.

POSTOPERATIVE GROIN NODE IRRADIATION There has been uncertainty regarding the indications for postoperative groin irradiation. Patients with histologically negative groin nodes or those with one small unilateral groin metastasis are at very low-risk of developing regional, pelvic or distant recurrences. Thus, adjuvant radiation therapy is probably of no therapeutic value (35). However, in view of the high incidence of regional, pelvic and distant failures in patients with large and/or two or more small groin metastases, postoperative groin irradiation with or without concurrent chemotherapy appears to be justified. Lymphadenectomy alone is probably not curative in patients with fixed or ulcerated groin node metastases (bulky N2 or N3 groin nodes), whereas groin lymphadenectomy and postoperative groin irradiation has been shown to decrease regional recurrence and improve survival (11, 16, 35, 46). *Hacker* (47) does not advocate full inguinofemoral lymphadenectomy in addition to the dissection all the enlarged nodes in the presence of bulky positive groin node(s) prior to radiation to avoid severe leg edema. Recent studies (48-49) show that not only the number of the positive nodes as well as whether they are microscopic or bulky, but the size of the small and the anatomic structure of the lymph node metastases have prognostic significance. The 5-year survival of metastatic groin nodes <5 mm, 5-15 mm and >15 mm were 91%, 42% and 21%, respectively (48). A significant difference in survival has also been reported according to the presence or absence of extracapsulal involvement of the metastatic nodes; patients with extracapsulal spread did significantly worse (48-49). The prognosis seemed to be related to the size within the lymphatic secondary with a significantly decreased survival when >50% of the node was occupied by the tumor cells in patients with one positive groin node (49).

THE ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF PELVIC LYMPH NODES Most reports (13, 50-53) strongly suggest that pelvic node metastases are rare in the absence of positive groin nodes regardless of the location of the primary tumor, and patients with one or no microscopically positive groin node do not require any further therapy including treatment of the pelvic lymph nodes. In the UCLA series (54) no positive pelvic node was encountered in patients with two or less unilateral groin nodes. Location of the pelvic nodal metastasis has been reported to be invariably on the same side as the positive groin nodes (50, 54-56). Unfortunately, none of the imaging techniques are reliable in evaluating pelvic lymph node metastases, although enlarged pelvic nodes are readily picked up by CT or abdominal ultrasound scanning. Microscopic nodal involvement might be diagnosed using pelvic lymphangiography. *Hacker et al.* (54) reported no positive pelvic nodes in patients without clinically suspicious or evident groin lymph nodes. Thus, careful preoperative assessment of the inguinofemoral nodes is one of the most accurate predictors of metastasis to pelvic nodes. Other reports (35), however, did not confirm this finding.

Extension of the radiation field to the pelvic nodes is probably associated with increased treatment morbidity. In the past, primary pelvic radiation combined with elective groin radiotherapy has been proposed irrespective of the groin nodal status. Currently, there is no evidence to substantiate this approach (18). Treatment of the pelvic nodes seem to be indicated only in patients with enlarged and/or two or more microscopi-

cally positive groin nodes. This should be ipsilateral in the presence of unilateral groin node involvement. Radiotherapy to the pelvic nodes is administered in combination with groin irradiation following wound healing, in general, within six weeks postoperatively.

PELVIC LYMPHADENECTOMY VERSUS POSTOPERATIVE PELVIC RADIATION As pointed out above, routine pelvic lymphadenectomy has no place in the management of squamous cell carcinoma of the vulva (1). It may be an alternative to postoperative pelvic irradiation in high-risk patients. The literature data on the efficacy of postoperative pelvic irradiation combined with inguinofemoral radiation treatment in patients at high-risk, i.e. with grossly positive and/or two or more small positive groin nodes are controversial. The Gynecology Oncology Group studied 114 patients with vulvar cancer and histologically proven positive groin nodes who were randomized to either radiation therapy to the groin and pelvis or pelvic node dissection. In this prospective study the relative two-year survival was superior for the group of patients receiving radiation therapy. The major survival advantage for radiation therapy was in patients with either clinical N2 and N3 or two or more microscopic positive groin nodes. Adjuvant radiation was more effective in reducing the incidence of groin recurrences. The beneficial effect of pelvic irradiation was not evident, in fact, less recurrence occurred in the lymphadenectomy arm. *Kucera and Weghaupt* (18) do not recommend elective pelvic node radiation because of the poor general condition and advanced age of the patients. Other investigators (19, 40, 57), however, are in favor of radiating the whole pelvis or the pelvic nodes in addition to groin node radiation therapy. *Boronow et al.* (58) did not report on pelvic recurrences after pelvic irradiation as integrated part of combined surgical and radiation therapy. In view of *Hacker* (47), radiation therapy is unlikely to sterilize enlarged pelvic nodes. He recommends to remove any enlarged pelvic nodes without full pelvic node dissection via separate incision prior radiation therapy.

At present, the therapeutic value of postoperative pelvic node radiation in vulvar cancer remains unknown. Considering pelvic node radiation one should keep in mind that pelvic lymphadenectomy adds nothing to the cure of patients with histologically negative pelvic nodes and it is of little value in patients with pelvic node metastasis (35). In addition, this procedure may be associated with a slight increase in operative morbidity and occasional mortality.

RADIATION THERAPY ALONE Apparently, there is no place for curative radiotherapy alone in the management of *early carcinoma of the vulva* unless the patient is unfit for surgery. However, this is very uncommon. In the authors series, in accordance with the literature data, wide local excision of the primary could be accomplished even in patients with severe medical problems.

Although there is a dearth of information, the results of radiation therapy alone in *advanced carcinoma of the vulva* have been discouraging and are inferior to those of combining radiation with conservative surgery (59). With radical radiotherapy alone approximately 40% local control rate can be expected (6, 60). Complete response to radiation therapy does not result in local control in all instances. As mentioned above, residual disease is not infrequent in the tumor site, thus, removal of the tumor bed has been advocated. Local excision of the residual tumor or tumor bed, in general, is a simple procedure, which can be carried out even in frail patients. *Thomas et al.* (61) suggest irradiation with or without chemotherapy as definitive management for those with midline vulvar lesions such as clitoral, vaginal and anal lesions where surgical removal is accompanied by major cosmetic and functional morbidity. In the authors' view this approach deserves further studies before one can embark on that strategy. For patients with large vulvar cancer radiation treatment alone is rarely curative.

In contrast to microscopic *nodal involvement*, clinical N2 and N_3 groin nodes can rarely be treated effectively with radiation alone. *Backström et al.* (11) reported on one patient with N3 groin node cured by radiation alone. Surgical excision of N2 or N3 groin nodes, in conjunction with radiation, has been recommended. *Henderson et al.* (20) do not advocate treatment of clinically positive groin nodes by irradiation alone since the high-dose that required will produce fibrosis in a substantial number of patients. In the absence of clinically enlarged node, groin node dissection has not been recommended to reduce the incidence of lymphedema associated with inguinofemoral lymphadenectomy and radiotherapy.

Radiation therapy alone may be used effectively as a palliative measure to relieve symptoms. Even cure has been reported on in this group of patients (41).

CHEMORADIOTHERAPY OF PRIMARY VULVAR CANCER The most frequently used agents in squamous cell vulvar cancer are cisplatin, 5-fluorouracil, mitomycin-C and bleomycin. Exclusive chemotherapy in vulvar carcinoma has failed to show any significant advantage (62). These agents, however, have been demonstrated in vitro and in clinical trials to increase the sensitivity of the squamous cancer cell of the vulva to radiation therapy (63). Recent evidence suggests that paclitaxel increases the sensitivity of vulvar carcinoma cell lines to radiation in vitro (64).

EARLY STAGES As with radiation, chemoradiotherapy has no established place in the management of early stage squamous cell carcinoma of the vulva. This may be beneficial in patients with midline tumors to permit more adequate local excision and organ sparing. *Lupi et al.* (65) believe that in pathologic complete responders surgery may be spared.

LOCALLY ADVANCED LESIONS Following the pioneer report by *Nigro et al.* (66) on the encouraging experience in treating

squamous cell anal carcinoma with preoperative chemoradiation therapy, high response rate to chemoradiotherapy in locally advanced carcinoma of the vulva has been reported (61, 67-71). *Whitaker et al.* (72) reported a pilot study of chemoradiotherapy in advanced carcinoma of the vulva. This study has recently been updated (73). Thirty-seven patients with advanced tumor (19 primary and 16 recurrent), that would have necessitated exenterative surgery were treated with chemoradiotherapy (mitomycin-C and 5-FU) and with surgery reserved as salvage treatment at 3 months after completion of treatment in those failing to enter complete remission. The local control rate was high in complete responders although the follow-up might not be long enough to draw final conclusions. The outcome for those patients failing to obtain complete response was disappointing. Whether it is due to the 3-month interval before performing surgery has jet to be determined. More probably, it is attributable to the biological behavior of the tumor. In general, surgery is carried out 4 to 6 weeks following radiation or chemoradiotherapy in order to allow healing of the local reactions and further regression of the tumor. *Berek et al.* (74) reported 83% 3-year survival rate in 12 patients with advanced disease treated with preoperative chemoradiotherapy (Cisplatin + 5-FU). *Thomas et al.* (61) using mitomycin-C, 5-FU and continuous radiotherapy reported on 6 clinically complete response of 9 patients with advanced disease. Three of them subsequently experienced local recurrence. Local recurrence may occur in pathologically complete responders diagnosed by multiple biopsy of the tumor side. These findings are in favor of excision of the tumor bed following complete disappearance of the primary tumor. *Sebag-Montefiore et al.* (73) has challenged this concept and believe that the high local control rate of the primary and recurrent disease in pathologically complete responders might not justify excision of the tumor bed, thus, sparing patients from surgery altogether. *Lupi et al.* (65) reported 31 patients with T3-T4N2 primary (24 cases) or recurrent (7 cases) vulvar cancer treated with concurrent chemoradiotherapy (mitomycin-C + 5-FU and pelvic radiation) followed by radical surgery. They achieved 42% clinical complete remission (pCR was 36%). It is noteworthy the chemoradiation was effective in eradicating regional and pelvic lymph node metastasis in a substantial number of patients. The actuarial 5-year survival rate was 55%. The toxicity and operative morbidity and mortality were acceptable in all but those patients with recurrent disease. *Russell et al.* (75) reported on 80% clinical complete response in 25 women with advanced disease. Treatment with the combination of bleomycin and radiation has resulted in unsatisfactory outcome (76).

In conclusion, chemoradiotherapy is safe but not without toxicity. The overall response rate is high (>90%) with complete response rates of 40-80%. Combining chemoradiation with surgery approximately 80% local control can be achieved, avoiding exenterative procedures in almost all instances. Chemoradiotherapy is effective in treating positive lymph nodes. Whether these can be translated into long-term survival benefit is not clear.

RECURRENT DISEASE Vulvar recurrences can be treated with some effectiveness using radiation therapy (11, 41-42). For small vulvar recurrences (T1 or T2 recurrent tumor) wide surgical excision with or without adjunctive treatment has been advocated (77). Wide local excision alone has been reported to be successful for isolated skin bride recurrences as well provided surgical margins are adequate (78-79). Inadequate margins require adjunctive radiation therapy (80). Prognostic factors adversely associated with survival include early (<1-2 years) recurrences, positive groin nodes at the time of primary surgery and recurrences outside of the primary location of the vulva (81-82). Local excision of large vulvar recurrence (>5 cm) has been commonly associated with local failure. Adjuvant radiotherapy and or chemotherapy has been used. The outcome for patients with recurrence outside the primary vulvar site is poor irrespective whether it is treated with surgery alone or with combined approaches. For patients with tumors extending to the urethral or perennial area primary radiation therapy has been recommended, which may be followed by local resection of the tumor bed 4 to 6 weeks after irradiation. The residual tumor should be locally excised in an attempt to cure the patients. As with locally advanced primary tumor, some locally advanced recurrent disease, although rarely, may require exenterative surgical procedure. Again the major prognostic factor in terms of disease control is the nodal involvement (27, 32).

Re-irradiation of a recurrent vulvar lesion may also be effective in a small subset of patients. The longer the disease free interval prior to the development of recurrent tumor the better the results of re-irradiation.

Chemotherapy is ineffective in local recurrence previously treated with radiation therapy with or without concurrent chemotherapy. Chemoradiotherapy has been reported to have a place in the management of local recurrence following vulvectomy or wide local excision (73). There has been increasing evidence to show that with chemoradiotherapy with or without surgery local-regional control can be achieved in a high proportion of recurrent disease (65, 73).

The curative value of *radiation therapy* for nodal relapse is limited because both local and distant failure is common in this group. To improve local control of the recurrent groin disease surgical excision of the enlarged node(s) should be performed if feasible. In spite of this, the prognosis has been uniformly poor. Thus primary control of the vulvar cancer and the regional nodes is of paramount importance. Recent reports on *chemoradiotherapy* seem to suggest the efficacy of this approach in eradicating both groin and pelvic node metastasis in patients with recurrent disease

TECHNIQUE AND DOSAGE OF IRRADIATION

PRIMARY TUMOR External beam therapy seems to be probably more effective than brachytherapy or implants and carries less risk for side effects. The energy of irradiation is crucial. Only

high-energy photons from supervoltage machines (16, 44) and, perhaps high-energy electron irradiation (6) appear to be adequate for radiation treatment for vulvar cancer. Brachytherapy as a sole modality may be effective in controlling small volume disease only. Combination of local irradiation with external irradiation does not seem to improve treatment results unless the proximal half of the vagina is involved because vaginal carcinoma does seem to be as radiosensitive as vulvar cancer (16). Nevertheless, intracavitary irradiation or implants can be used as a boost to external therapy.

Hacker et al. (16) recommended that external radiation to the primary tumor should be delivered through parallel opposed (AP) anterior and posterior (PA) pelvic portals, with both fields being treated daily in an isocentric fashion. This will deliver a relatively homogeneous dose of irradiation to the vulva, vagina and rectovaginal septum but not to the pelvic lymph nodes. Should the groin and pelvic nodes be encompassed in the irradiation field the AP and PA portals can be enlarged. Others (10, 41) are in favor of using perennial portals. Frog leg position of the patient also has support (59).

The recommended dosage for small tumors is usually 50 Gy, with daily fraction size of 1.8 Gy or less. *Thomas et al.* (83) reported minimal late sequelae in patients treated with 1.75 Gy or less daily fractions. *Pao et al.* (59) found no dose response for subclinical disease between 45 and 75 Gy. To achieve complete regression of large primary tumors higher doses (up to 85 Gy) should be administered (15).

LYMPH NODES A variety of techniques has been used to give inguinal lymph node irradiation. *Henderson et al.* (20) recommended the method of two separate anterior shaped fields. *Simonsen et al.* (84) are in favor of using a single field technique.

The fields of radiation should encompass the superficial and deep inguinal-femoral nodes with an appropriate safety margin, perhaps extending to the margin of the vulvar excision. Whole pelvis radiation therapy may be administered to treat both groins and obturator, external and internal iliac areas, via either 4-field box technique or AP and PA opposed fields.

The most commonly used tumor dose at 2 to 3 cm depth is 45 to 50 Gy in five weeks, with 1.8-2 Gy per fraction (12, 18-19). According to *Henderson et al.* (20) the minimum lymph node dose should not be less than 50 Gy. *Simonsen et al.* (84) recommended higher dose in patients with perinodular growth. Patients with grossly positive nodes require a higher dose unless the enlarged nodes are dissected. Should regional postoperative radiotherapy is indicated, the routine use of midline block has not advocated (85).

The energy of radiation depends on the amount of the overlying subcutaneous tissue. Very high energy irradiation may underdose superficial lymph nodes that lie immediately under the skin, e.g. in thin patients. Although most authors have utilized telecobalt, telecesium or x-ray therapy there seems to be an advantage of combining photon therapy with electron radiation. However, the use of electrons for the entire treatment has not been recommended because moderate to severe skin and subcutaneous changes will occur with high-energy electrons (20).

COMPLICATIONS OF RADIATION THERAPY

RADIATION OF THE VULVA Orthovoltage treatment of the primary tumor has been associated with severe complications, mostly necrosis (17, 86). The use of electron irradiation alone to treat vulvar cancer carries a relatively high risk of severe complications (6). With the advent of megavoltage machines, newer technology in radiation planning and delivery, severe complications such as *vulvar fibrosis and necrosis* are uncommon. Their appearance is related to the daily fraction dose and total dose of radiation. In contrast, *moist desquamation* of the skin is not infrequent and usually appears after the vulva has received a dose of 30 to 45 Gy, necessitating a short treatment interruption (16, 61). Considerable skill is required from trained nurses to manage this complication. Other mild adverse effects include *erythema, atrophy* and *telangiectasis. Thrombo-embolic disease, fistula formation* and *stenosis of the introitus* are rare. *Myelosuppresion* is also infrequent and usually mild.

GROIN IRRADIATION Acute side effects of inguinal irradiation have been limited to dry and occasionally small patches of moist *desquamation of the skin. Inguinal fibrosis* is dose dependent and usually mild to moderate and asymptomatic in most cases. This side effect is uncommon if the dose is less than 50 Gy. Patients with a marked amount of subcutaneous fat are particularly apt to develop fibrosis (20). The risk of *lymphedema* is extremely low with most series of no such complications. A *vascular necrosis* of the thigh with or without femoral neck fracture is a major worry which has been reported to occur at doses as low as 26 Gy to the femoral head. The cumulative actuarial incidence of femoral neck fracture following groin irradiation was 11% at 5 years and 15% at 10 years and was related to dose, cigarette use and x-ray evidence of osteoporosis prior to radiotherapy (87). This sequel seems to inevitably occur in some patients treated with pelvic irradiation. Nevertheless, care should be taken to minimize the dose to the femoral base where possible, e.g. by shielding the femoral neck, without compromising treatment results. This may be achieved by delivering a portion of the inguinal lymph node treatment with electrons (20, 87). Major *bowel complication* has been reported on in a few patients treated with pelvic irradiation (41) or with chemoradiotherapy (73).

Combination of surgical and radiation treatment of the groin nodes does not seem to increase the complication rate (22, 35). In contrast, *Hacker* (47) reported severe leg edema after full inguinofemoral node dissection combined with groin irradiation. Wound healing is probably not altered by pre- or postoperative irradiation.

Close evaluation of the patients throughout and following irradiation as well as optimal skin care including taping the skin fields apart, keeping intact skin dry without using ointment, and perennial hygiene are important to avoid side effects and decrease the need for interruption of treatment. Counseling prior to radiation to improve the tolerance of radiation is also important for vulvar skin reaction which is probably inevitable. Moist desquamation responds well to local antiseptics and topical cortico-steroids.

CONCLUSIONS The role of radiation therapy in the management of vulvar cancer has not been adequately explored. The evidence available suggests that irradiation in combining with surgery may improve treatment results and quality of life.

The management of patients presenting with early stage disease has been surgical with satisfactory outcome in terms of local control and long term survival. There is no place for radiotherapy in small stage I and II squamous cell carcinoma of the vulva unless the tumor is located on the perineum or clitoris. T1 and T2 lesions encroaches on either the perineum or clitoris may well be treated with preoperative irradiation or chemoradiotherapy to bring about tumor shrinkage and thereby permitting tissue sparing surgical excision.

Elective groin irradiation replacing inguinofemoral lymph node dissection combined with surgical excision of the primary tumor has not been practiced in routine setting.

As stated by *Neville Hacker* (47): "with the experience now accrued, preoperative radiation, with or without concurrent chemotherapy, should be regarded as the treatment of first choice for patients with advanced vulvar cancer who would otherwise require some type of pelvic exenteration." Pelvic exenteration is rarely indicated. It is a viable option when organ-preserving treatment, i.e., preoperative radiation with or without chemotherapy has failed. The combined approach as opposed to exenterative surgery is significantly superior in terms of survival in patients with positive groin nodes. Whether the tumor bed should be excised in those patients with locally advanced primary tumor who obtain complete remission following radiation or chemoradiotherapy is not clear and requires further studies. The author is in favor of excising the tumor bed.

Most patients with isolated small vulvar recurrence can be saved with further surgical excision. More advanced local recurrent tumor, however, require radiation or chemoradiotherapy to avoid exenterative procedure. Residual tumors in those without pathologic complete remission and perhaps, the tumor bed in complete responders should be excised. Further studies are needed to determine the long-term outcome of radiation therapy alone or chemoradiotherapy without subsequent excision of the tumor site in those with pathologic complete response.

Radiation therapy is commonly associated with toxicity including both acute and late complications, the latter being more severe. The major acute toxicity is the development of perennial moist desquamation, often resulting in treatment delay. With the advent of megavoltage machines, newer technology in radiation planning and delivery, severe complications such as vulvar fibrosis and necrosis are uncommon.

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