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STAGE I SQUAMOUS CELL CARCINOMA OF THE VULVA

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Abstract

Eighty-six patients with invasive squamous cell carcinoma of the vulva stage I were followed for 2 to 20 years after surgical treatment varying from local excision to radical vulvectomy with inguinal lymph node dissection. The results are presented and the prognosis discussed in relation to the radicality of the surgical intervention, the degree of tumour differentiation, the morphologic properties of tumour cell population, and the tumour host relationship. The most important prognostic factor seemed to be the radicality of the surgical intervention. To reduce patient morbidity in radical surgery while still achieving a comparable survival rate an operative approach with less than radical vulvectomy, inguinal dissections or pelvic lymphadenectomy, or both, is proposed for selected patients.

Vulvar carcinoma stage I is defined by the FIGO classification as including tumours with a diameter of up to 2 cm and without palpable lymph nodes in the groin, or with palpable lymph nodes judged at a clinical evaluation as not giving metastases.

This definition has been criticized on the grounds that the depth of infiltration ought to be specified, and that the limit of tumour size, i.e. 2 cm in diameter, has not proved to be satisfactory for prognostic evaluation (2, 9, 10, 12, 20, 22).

Various treatment modalities for stage I vulvar carcinoma have been suggested (5, 6, 9, 12, 17, 18, 20, 27). A number of authors have attempted to use histologic parameters such as depth of tumour growth and occurrence of vascular invasion (3, 4, 12, 20, 27) in order to achieve more individualized and less traumatic therapy than the generally ac-

cepted measures used today for all stages of squamous cell carcinoma of the vulva, namely vulvectomy and lymphadenectomy, which appear to be too extensive and unnecessarily aggressive for these early tumours.

The present report describes an investigation carried out to analyse the results of therapy obtained in vulvar squamous cell carcinoma stage I, and to evaluate the clinical and histologic factors which may have bearing on the prognosis, leading to more differentiated forms of treatment.

Material and Methods

A total of 317 patients with malignant tumours of the vulva were referred to this hospital during the 20 years between 1960 and 1979. The diagnosis of squamous cell carcinoma was confirmed in 266 of these patients, of whom 86 were classified as being in stage I. These 86 patients constitute the basis for the present report.

The average age was 65 years (range 35–86 years, median age 66 years). About 25 per cent of the patients had been treated previously for vulvar disease, especially for lichen sclerosus and hyperplastic dystrophy. Nine patients (10%) had some other malignant disease in their case histories (4 cancer mammae, 2 cancer colli uteri, 2 cancer cutis, 1 cancer coli).

The most common initial symptom noted was

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itching or pain, or both, reported by 42 patients (49%). Thirty-two patients (37%) first noted palpable hardening of tissue, or sores, while 7 (8%) had bleeding initially. Five patients could not state the primary symptom.

Delay in seeking medical aid after the onset of symptoms varied between two weeks and ten years: 51 (59%) 0 to 6 months, 13 (15%) > 6 to 12 months, 16 (19%) > 1 to 5 years, 6 (7%) more than five years.

The tumour was located in the labia majora pudendi or the labia minora pudendi in 47 patients (55%), in the area around the clitoris in 26 cases (30%) and in the posterior commissurae in 4 patients (5%). In 9 cases (10%) the exact site of the primary tumour could not be established.

Surgery had been performed as partial or radical vulvectomy utilizing electro-resection with the open-wound technique (24). Radical vulvectomy was performed in 78 patients, partial vulvectomy in 6 cases and local excision alone in 2 patients.

About 8 weeks after the radical vulvectomy, groin dissection was performed in 35 of the 78 patients. In one patient, the groin dissection was supplemented by pelvic lymphadenectomy. In 68 (87%) of the 78 patients, external irradiation was applied to the inguinal regions in connection with the vulvar surgery.

A ^{137}Cs unit was used with single-field technique, with a field size of 8 cm \times 13 cm and SSD = 20 cm. The peak absorbed dose was 7 Gy per fraction, with 3 fractions a week up to a total of 21 Gy, given before the lymphadenectomy. The deepest part of the target, representing the inguinal nodes, was assumed to be located 3 cm below the skin surface, obtaining a target absorbed dose (specification point on the central axis at the centre of the target area) of about 17.6 Gy. Patients not operated upon with groin lymphadenectomy have during recent years with increasing frequency been given additional irradiation. Of these 43 patients 21 were given a target dose of 17.6 Gy and 15 a target dose of from 21 up to 38 Gy. Seven patients were not given irradiation at all.

When metastatic nodes were detected microscopically in the surgical specimens, the inguinal region and the pelvic nodes on the respective side were given additional external irradiation using a ^{60}Co unit with single-field technique and SSD = 80 cm, with a field size of about 150 cm². The peak absorbed dose was 3 Gy per fraction, and 5 fractions a week were given up to a total peak absorbed dose

of 24 or 33 Gy, depending on the findings in the surgical specimens (metastatic malignancy limited to the nodes, or growing also outside the nodes). The deepest part of the target, representing the operation area, the external and the interiliac lymph nodes, was assumed to be located 10 cm below the skin surface, resulting in a target absorbed dose (specification point on the central axis at the centre of the target area) of about 19.2 or 26.4 Gy.

All surgical tissue specimens were fixed in formol and further embedded in paraffin. The specimens were re-examined and classified by the same pathologist.

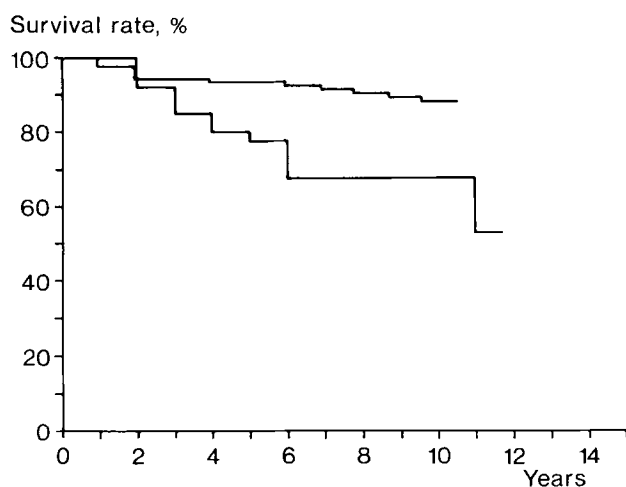
The degree of differentiation (well, moderately or poorly differentiated) was based on the least differentiated elements in the specimens (1). In 77 patients the prognoses were estimated from properties of the tumour cell population: structure, differentiation into cell type, nuclear polymorphism, mitosis, and the tumour host relationship: mode of invasion, stage of invasion, vascular invasion, (lymphotic) cellular response, were graded according to a point-score system used for squamous cell carcinoma of the larynx (13, 14), the palate (8), the gingiva (28), the uterine cervix (25) and the vulva (15). Each parameter was given 1 to 3 points resulting in a total of 8 to 24 points in an increasing grade of malignancy. The total point-score values were compared with 5-year crude survival to find out whether the point-score system could be used for prognostic purposes also in stage I vulvar squamous cell carcinomas. In 4 cases the histologic specimens could not be refound and in 5 cases they were not evaluable.

The surgical intervention was defined as radical if the distance from the tumour to the resection margin as judged from the histopathologic examination exceeded 1 cm; if it was 1 cm or less, the radicality was considered dubious. Tumour growth in the resection margins meant a non-radical intervention. Treatment failures recorded in the perineum, the vulva, the lower half of the vagina or in the urethra were classified as local recurrences. Metastases to groin lymph nodes or pelvic wall lymph nodes, or both, after completion of treatment were defined as regional metastases. Spreading to organs outside the small pelvis was defined as distant metastases.

The prognosis was defined in terms of 5-year survival according to life-table analysis. Multivariate analysis by Cox's proportional hazards model was used for working out the scoring system.

Table 1
Primary treatment technique and type of treatment failure

Primary treatment technique	No. of cases	Local recurrences	Regional metastases	Local recurrences and regional metastases	Death in carcinoma ≤ 5 years
Hemivulvectomy	6	1	-	-	-
Vulvectomy	43	6	-	-	-
		-	5	-	4
		-	-	3	1
Vulvectomy and groin dissection with metastases	7	-	-	2	1
Vulvectomy and groin dissection without metastases	28	5	-	-	-
		-	2	-	2
Local excision	2	1	-	-	-



Median survival (lower curve) for stage I: 11.0 years (n=86).

Results

The prognoses calculated by life-table analysis are shown in the Figure. In the 67 patients for whom 5-year survival could be calculated, 6 died from the malignant disease and 7 from intercurrent disease; the 5-year crude survival was 81 per cent. Two of the 6 patients who died from carcinoma within five years had had symptoms for more than 6 to 12 months before the beginning of treatment, and 4 had had symptoms from 1 to 5 years before therapy. Three of the patients had tumour in the clitoris region and the other 3 had tumour in the labia minora pudendi or in the labia majora pudendi.

Of 8 patients who died from carcinoma after periods of observation varying from 2 to 5 years, 5

had undergone radical vulvectomy and received irradiation of the groins. Three had had radical vulvectomy, radiation therapy of the groins and inguinal lymphadenectomy.

Survival rates and the frequency of recurrences and metastases in relation to primary surgery appear in Table 1.

Local recurrences were recorded for 18 patients (21%) and in 8 of these the primary surgical treatment was of doubtful radicality or non-radical. The corresponding figure for the 68 patients without local recurrences was 12. Five of the 8 patients who died from carcinoma were judged as non-radical or of doubtful radicality.

One of the two patients treated with only local tumour excision was further treated with radium needles implanted in the area of the incision. Two years later she underwent vulvectomy and bilateral groin dissection because of local tumour recurrence. No metastases were found in the excised lymph nodes. This patient was still alive after an observation period of 16 years.

Metastases in the surgical lymph node specimens were found in 7 (about 20%) of the 35 patients in whom lymphadenectomy was performed. Four of the patients had their primary tumour in the area of the clitoris (2 with metastases on the right side and 2 with metastases on the left side), and 3 on one side of the labia majora or minora pudendi and with ipsilateral metastases in the groin. In one of the patients with metastatic nodes on the left pelvic wall, the pelvic nodes were removed but not radically. The primary classification of her disease had

been incorrect in this patient. A lymph node of about the size of an almond was found in the left groin, but was considered to be merely due to inflammation. She lived for 18 months after completion of treatment, although with regional and local progression of the tumour. One patient had regional metastases concomitantly with a local tumour recurrence.

Two of the 28 patients without metastatic malignancy in the excised lymph nodes (about 7%) later displayed metastases in the inguinal regions. It was at the same time found that local recurrence had occurred in these two patients.

Eight of the 43 patients (about 19%) who underwent radical vulvectomy, without additional lymphadenectomy, were later found to have metastases in the groins. Three of these patients had simultaneous local tumour recurrences. In 4 of these patients the lymph nodes were irradiated with an absorbed target dose of 17.6 to 21 Gy, but the other 4 had not received radiation therapy. Of the 28 patients in whom no metastases were recorded 25 received an absorbed target dose of 17.6 Gy, 3 received no irradiation of the inguinal regions. Of 7 patients in whom metastases were recorded, 5 were given additional irradiation with an absorbed target dose of about 19.2 Gy up to 26 Gy, 2 patients did not receive additional irradiation.

Five-year survival, lymph node involvement and recurrences in relation to the total point-score values are given in Table 2.

The 5-year crude survival for patients with varying degrees of tumour differentiation was 45 of 54 patients with well differentiated, 4 of 7 with moderately differentiated, and 4 of 6 with poorly differentiated tumours. These differences are not significant. No differences were noted in frequency of tumour recurrence and metastases between groups with different tumour differentiation. It was not possible, from the point-score values, to divide the material into various patient groups with different prognoses. However, a positive correlation existed between local recurrences and scoring values ($p < 0.03$).

Multivariate analysis of the different parameters used in the point-score values showed the mode of invasion to be the most important one ($p < 0.001$). Six local recurrences (about 12%) were reported among the 49 patients with a score of one point and ten local recurrences (about 30%) among those with a score of at least two points.

Among the 7 patients with lymph node metastases

Table 2

Point-score values in relation to death in carcinoma, lymph node involvement and recurrences

Total point-score values	No. of cases	Lymph node metastases with primary treatment	Local recurrence	Re-regional recurrence	Death in carcinoma ≤ 5 years
8	2	-	-	-	-
9	5	-	-	-	-
10	4	-	-	-	-
11	13	-	-	-	-
12	15	1	4	2	-
13	6	2	-	-	-
14	9	-	4	4	4
15	5	-	1	1	1
16	2	2	1	2	1
17	4	-	1	-	-
18	4	-	1	1	1
19	5	1	2	1	1
20	1	-	1	-	-
21	2	1	-	-	-
22	-	-	-	-	-
23	-	-	-	-	-
24	-	-	-	-	-
Total	77	7	15	11	8

the point-score value for vascular invasion was at least two points (implying a high likelihood of vascular invasion).

Discussion

The initial symptoms of vulvar carcinoma are often mild and therefore ignored by the patient. A long history of disease before diagnosis implies a poorer prognosis, as the tumour is then at an advanced stage. The survival rates in the present material are about the same as those reported by other authors (2, 10, 12, 27).

Opinions differ as to whether tumours in the clitoris area are more aggressive than in other locations and have a poorer prognosis (2, 9, 18, 20, 21, 22). The present series of stage I tumours as well as another larger material including stages I-IV tumours (23) showed only a slightly poorer prognosis and a slightly higher rate of recurrence and metastases for tumours near the clitoris. It is probable that tumours located in the midline can spread to one or both sides of the inguinal regions. Metastasizing from unilateral tumours to the contralateral groin was not recorded in this material. This agrees with

several other reports (11, 16, 19), although metastasizing to the contralateral groin has been noted in some other investigations (7, 26).

The importance of radicality at surgery of the primary tumour is evident from the figures of recurrence rates, which were considerably higher (8/20) among patients operated upon non-radically or with doubtful radicality than among those initially submitted to radical excision of the primary tumour (10/66). This is in line with previous findings.

Metastases in the regional lymph nodes were found in 8/43 (about 19%), 2/28 (about 7%) and 1/6 patients following different modes of therapy such as irradiation alone, preoperative irradiation where no metastatic growth was found in excised tissues, or pre- and postoperative irradiation in cases where radical surgery had demonstrated metastatic growth in the groin lymph nodes. The material is small and the patient groups included (i.e. only radiation treatment or irradiation in combination with surgery) are not strictly comparable.

Radiation therapy alone does not, however, give satisfactory results with the patient selection and with the absorbed doses used in the present investigation.

In the present material, moderately and poorly differentiated tumours did not have significantly poorer prognoses than well differentiated ones. Nor were important differences seen for local and regional treatment failures. This agrees with most reports (12, 18, 20), although a significantly poorer prognosis for poorly differentiated tumours has also been suggested (26).

Some authors (12, 18, 20, 27) have suggested that carcinoma on the vulva with less than 3 to 5 mm depth of invasion and without vascular channel involvement very rarely gives lymph node metastases.

A poorer prognosis could not be demonstrated with an increasing number of points in the scoring system. This contradicts the findings of KABULSKI & FRANKMAN (15), where a poorer prognosis was noted with an increasing number of scoring points. As this figure could not be reproduced in the present series the reason could be that only stage I carcinomas with a generally good prognosis were examined. The frequency of inguinal metastases did not increase with increasing numbers of points, either. However, more recurrences were noted in patients with high scorings; no patient with a point-score value of less than 14 points died of the disease

before 5 years, and no patient with a point-score value of less than 12 points had lymph node metastases at the primary treatment or later had recurrence. Making comparisons, however, it would appear that the degree of radicality of the surgery is the more important parameter for the prognosis.

Conclusions. Radical vulvectomy is a rational form of treatment of the primary tumour. Repeat operation should be considered if the initial measure was non-radical or of doubtful radicality.

Ipsilateral groin lymph node dissection is sufficient for tumours limited to one side of the vulva. Midline tumours require bilateral groin dissection. Pelvic lymphadenectomy is not indicated.

The not very aggressive irradiation of the groins used in the present series is not sufficient as the only mode of treatment.

The methods of selection, the grading of tumour differentiation and the point-score system used in this investigation are not adequate for working out differentiated treatment schemes.

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