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COMBINED BLEOMYCIN AND IRRADIATION IN PREOPERATIVE TREATMENT OF ADVANCED SQUAMOUS CELL CARCINOMA OF THE VULVA

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Forty-two patients with advanced squamous cell carcinoma of the vulva were treated with a combination regimen of bleomycin 180 mg and external irradiation 30–45 Gy. Twenty patients had primary lesions, and 22 patients had recurrent disease. Fifteen (75%) of the patients with primary disease showed objective response (five complete and ten partial response). Four underwent surgery. Of these, one is alive after 60 months with no evidence of disease. Two have died of unrelated causes without signs of recurrence. Seventeen relapsed and died of carcinoma of the vulva. Median survival for patients treated for primary disease was 8.0 months. Thirteen (59%) of 22 patients treated for recurrence showed objective response (two complete and eleven partial responses). None underwent surgery. All these patients died of carcinoma of the vulva. Median survival was 6.4 months. Toxicity was acceptable, and there were no treatment-related deaths. Even taking into account that our patients had very advanced disease, the results are disappointing. An increase of the radiation dose beyond the maximum of 45 Gy given, and more aggressive surgery, might have improved the results.

Advanced-stage squamous cell carcinoma of the vulva is a difficult clinical problem. According to FIGO Annual Report No. 21 (1) the 5-year crude survival is 37% in stage III and 21% in stage IV. When there are histopathologically verified metastases in the inguinal nodes, the 5-year crude survival drops down to around 15% in stage III and 4% in stage IV. Surgery in these situations often requires some form of pelvic exenteration, with associated high morbidity and mortality, to achieve local control. Several authors have reported the effective use of preoperative irradiation to reduce tumor volume and allow less aggressive surgery with preservation of bladder and rectum function. The rate of treatment-related complications has, however, been rather high (2–6). In 1975 we started a protocol for treatment of advanced primary and recurrent squamous cell carcinoma of the vulva with a combination of bleomycin 180 mg and irradiation, 30–45 Gy. This treatment regimen was based on data showing that bleomycin and irradiation had a synergistic effect on squamous cell carcinoma, and on some promising reports concerning bleomycin combined with irradiation in the treatment of squamous cell carcinoma of head, neck and larynx (7–9).

The patients included in the protocol had very advanced disease, and the regimen was expected to make only a proportion of the cases operable, whereas the rest were expected to be adequately palliated. In a preliminary report in 1982 (10) presenting the results of the first 13 patients treated (9 with primary advanced disease and 4 with large recurrences), promising results were found. The study was therefore continued, and up to 1987, 29 additional patients (11 with advanced primary tumors and 18 with large recurrences) had been treated. The intent of the present report is to evaluate the role of bleomycin/irradiation in the treatment of squamous cell carcinoma of the vulva.

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Material and Methods

From 1975 through 1987, 42 patients with advanced squamous cell carcinoma of the vulva were treated with

Table 1

Patient characteristics in 20 patients with primary advanced stage inoperable squamous cell carcinoma of the vulva treated with bleomycin combined with irradiation

Pat.	Age years	Histologic differentration	Clinical stage		Total dose of		Response	Surgery	Duration of remission (months)	Site of relapse	S (months)	Status
			FIGO	TNM	Bleomycin mg	Irrad. Gy						
1	82	W	IV	T3N3M0	45	30	SD		2	L + G	5	DOD
2	73	M	IV	T2N3M0	180	45	PR		1	L + G	5	DOD
3	65	M	IV	T4N2M0	180	30	PD		1	L + G + D	6	DOD
4	62	P	IV	T3N3M0	180	30	CR		3	L	12	DOD
5	79	P	IV	T3N3M0	180	30	CR		11	L + G	22	DOD
6	48	P	IV	T4N0M0	180	30	SD		1	L	5	DOD
7	60	W	IV	T4N2M0	180	30	CR	VG	17	G	22	DOD
8	61	M	IV	T3N3M0	180	30	SD		1	L + G	6	DOD
9	73	M	III	T3N0M0	180	30	PR		2	L	7	DOD
10	79	M	III	T3N2M0	120	30	PR	VG	—	—	58	DOC
11	77	M	III	T3N2M0	150	30	PR	VG	—	—	7	DOC
12	86	M	IV	T3N3M0	180	9	SD		5	L + G	11	DOD
13	62	M	IV	T4N3M0	180	30	PR		13	L	25	DOD
14	60	M	IV	T4N2M0	180	40	CR		9	L	17	DOD
15	68	M	III	T3N0M0	180	45	PR		1	L	8	DOD
16	78	W	III	T3N2M0	90	45	PR		3	L	7	DOD
17	58	M	III	T3N2M0	180	30	CR	VG	—	—	60	NED
18	69	M	IV	T3N3M0	90	40	PR		3	L	5	DOD
19	70	W	III	T3N2M0	180	30	PR		3	L + G	7	DOD
20	65	W	III	T3N1M0	180	40	PR		8	G	10	DOD

C_R = Complete remission
PR = Partial remission
SD = Stable disease
PD = Progressive disease
L = Local
G = Groin
D = Distant
VG = Radical vulvectomy + bilateral lymphadenectomy
DOD = Died of disease
DOC = Died of other causes
NED = No evidence of disease
S = Corrected survival
W = Well; M: moderately, and P: poorly differentiated carcinoma

bleomycin and irradiation at the gynecology department of the Norwegian Radium Hospital. Twenty patients had primary lesions, and 22 had recurrent disease. Age, histology and staging, FIGO and TNM, for the patients treated for primary disease are listed in Table 1. The mean age of these patients was 69 years with a range of 48 to 86 years. If the tumor was rendered operable after bleomycin/irradiation, surgery was done after 3 to 8 weeks. Patient age and the site and size of the tumor in the group treated for recurrence are shown in Table 2. Two patients had received postoperative radiotherapy due to metastases in the inguinal glands. In 14 patients the recurrence was localized to the vulva and/or the perineum, in 3 to the groin (unilateral) and in 4 both to the vulva/perineum and the groin (Table 2). In all these patients the tumor involved urethra, vagina or anus alone or in combination, or was fixed to the pelvic bones. In two patients the recurrence was localized to the pelvic wall (Table 2). Most of these were first recurrence; only three (patients No. 2, 3 and 22) were second recurrences. The mean age of these patients was 72 years (range 57 to 88 years). The criteria for response were defined as follows: Complete remission (CR)—total disappearance of all measurable lesions for at least one month; partial remission (PR)—at least 50% reduction in measurable tumor; stable disease (SD)—0–49% decrease in measurable tumor and no new lesions; and progressive disease (PD)—increasing volume of tumor or new lesions during treatment.

Radiotherapy consisted of external photon irradiation by a linear accelerator (7 MeV), a betatron (33 MeV) or a cobalt machine through parallel opposed anterior and posterior portals on alternative days to the vulva, inguinal regions and the pelvis. The radiation fraction size was 3 Gy per day, given 5 days a week. Total dose was 30 Gy. If surgery was not possible after the treatment, the radiation dose was increased to 34–45 Gy if well tolerated. Patients with extremely large tumors were given electron treatment to a vulval field.

Bleomycin 30 mg i.v. was given on days 1, 3 and 5 of the treatment to a total dose of 180 mg. Therapy was given in weeks one and three; in the second week the patients received no treatment. Treatment of only the opposing

Table 2

Patient characteristics in 22 patients with recurrent squamous cell carcinoma of the vulva treated with bleomycin combined with irradiation

Pat. No.	Age (years)	Histologic grade	Recurrence		Total dose of		Response	S (months)	Status
			Site	Size (cm)	Bleomycin mg	Irrad. Gy			
1	70	W	L	5	75	30	SD	5	DOD
2	82	W	L	5	180	30	CR	12	DOD
3	72	P	L	>12	180	30	PR	20	DOD
4	58	W	PW	10	180	40	SD	7	DOD
5	74	W	L	5	180	40	PR	5	DOD
6	68	M	L	7	180	30	SD	12	DOD
7	77	W	G	11	180	40	PR	7	DOD
8	68	M	L+G	4+2	180	30	PR	6	DOD
9	75	M	L	5	180	30	PR	7	DOD
10	88	M	L	6+3	120	30	SD	3	DOD
11	64	M	L	6	180	30	PR	2	DOD
12	82	M	L	12	30	6	PD	1	DOD
13	59	W	G	4	150	40	PR	15	DOD
14	74	M	PW	>6	90	50	SD	5	DOD
15	63	M	L	NM	180	30	CR	25	DOD
16	57	M	G	NM	180	30	SD	4	DOD
17	79	M	L	>12	180	30	PR	3	DOD
18	75	M	L	5	180	30	PR	3	DOD
19	87	P	L	5	180	45	PR	5	DOD
20	72	W	L	4	150	24	SD	9	DOD
21	76	M	L	6	180	30	PR	18	DOD
22	71	M	L	4+3	180	30	SD	14	DOD

L = Vulva and/or perineum
G = Groin
PW = Pelvic wall
NM = Not measurable
DOD = Died of disease
S = Corrected survival
W = well; M: moderately and P: poorly differentiated carcinoma

fields on alternating days was chosen for capacity reasons, and because treatment was not considered as definite therapy. The dose specifications refer to the midplane dose. For cobalt treatments the dose was somewhat higher close to the surface, and uneven fractionation will result in a 10–15% higher CRE-value in a standard 15 cm thick field, whereas homogeneity was better for the higher energies. Survival rates were calculated from the time of diagnosis using the methods of Kaplan & Meier (11).

Results

In 17 of the 20 patients treated for primary disease, and in 17 of those treated for recurrence, a total dose of bleomycin 180 mg and 30–45 Gy external irradiation were given. Three patients (two with primary disease and one with recurrence) received 90 mg of bleomycin only, due to protocol violations (Tables 1 and 2). Fifteen of the 20 patients treated for primary disease showed objective response, 5 (25%) CR and 10 (50%) PR. In 4 patients (20%) there was stable disease, and one had progression during treatment. The tumor was rendered operable in seven patients (35%); two with PR in addition to the five with CR. Three patients with CR were not fit for surgery because of generally poor condition. Four patients, two with CR and two with PR, underwent surgery. A radical vulvectomy and bilateral inguinal lymphadenectomy were done. Histologic examination of the operative specimen showed residual tumor and metastases to the inguinal glands in all four patients. Resection borders were free. Of the patients who underwent surgery, one had a recurrence in the right groin 17 months after treatment and died of bleeding from the femoral artery; two died of intercurrent diseases without signs of recurrence after 7 and 58 months respectively, and one is alive with no evidence of disease 60 months after treatment (Table 1). Eight of the 11 responding patients who were not operated on had groin metastases at the start of treatment. Response was seen both locally and in the groin. Five of these patients suffered a relapse in the vulva, three in the vulva and the groin. Of the three responding non-operated patients without groin metastases, two relapsed in the vulva and one in the groin (Table 1).

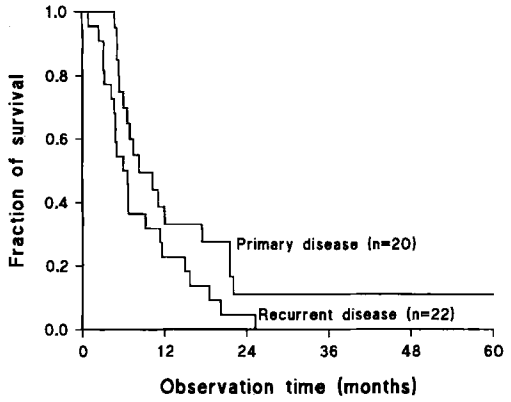

Figure. Survival curves of 42 patients with advanced primary and recurrent vulva carcinomas treated with bleomycin combined with irradiation.

Distant metastases were not seen at the time of relapse in any of these 11 patients. The patient with progressive disease developed lung metastases during treatment.

Median survival among patients treated for primary disease was 8.0 months (range 5–60+ (Figure)). Median corrected survival was 40 months (range 8–60+) for patients who underwent surgery and 7 months (range 5–25) for those who did not ($p = 0.001$). Histologic grade and clinical stage did not influence response rate or survival. Thirteen of the 22 patients treated for recurrences of squamous cell carcinoma of the vulva showed objective responses, 2 (15%) with CR and 11 (50%) with PR. In eight (36%) patients there was SD and one had PD, (Table 2). One of the patients with CR (No. 2) was 82 years old and was judged not fit for surgery, and in the other patient with CR (No. 15) the primary recurrence was multifocal and radical surgery was not possible. The tumors were not rendered operable in any of the 11 patients who achieved PR. However, in one of the patients (No. 21) local excision performed 9 and 15 months after treatment because of pain. Resection borders were free. Three months later she relapsed in the vulva and the recto-vaginal fascia, and posterior exenteration was performed. She died of postoperative complications. Two patients (Nos 3 and 22) underwent local excision 7 and 5 months after treatment respectively, but both relapsed locally and developed metastases in the groin shortly after surgery. Except for the patient who died postoperatively (No. 20), the patients in this group died in an often very painful situation with large, ulcerating and infected tumors.

Median survival among patients treated for recurrence was 6 months (range 1–25 months (Figure)). Histologic grade did not influence response or survival.

Toxicity. In 10 (50%) of the patients treated for primary disease and 12 (55%) with recurrence, side-effects were absent or very mild. In 3 patients bleomycin was stopped after 35, 40 and 120 mg respectively because of generalized exanthema. These patients also had fever and chills. In one patient the irradiation was stopped, and in two treatment was postponed because of soreness of the skin. In four patients chest x-rays suggested interstitial pneumonitis after a total dose of 180 mg of bleomycin. None of these patients showed clinical symptoms of lung disease. In three patients treatment was stopped because of generally poor condition. These patients were bedridden and senile at admittance with severe symptoms of their disease, and treatment waas started as a palliative measure. Detailed toxicity data are shown in Table 3.

Table 3

Toxicity observed in 42 patients

	WHO grade (number of patients)				
	0	1	2	3	4
Soreness	29	9	5	0	0
Fever and chills	35	1	2	4	0
Exanthema	38	2	0	2	0
Anorexia/fatigue	39	0	0	0	3
Pneumonitis	38	4	0	0	0
Alopecia	40	0	1	0	1
Nausea/vomiting	40	2	0	0	0

Discussion

In our sample of 42 patients, objective response was seen in 28 (67%). The response rate was higher in the group treated for primary disease than in the group treated for recurrrence—75% versus 59%. The tumor was rendered operable after treatment in 7 (35%) of the patients with primary disease. This is a high percentage, as all patients had very advanced disease (5 T4, 8 N3, Table 1). In the group treated for recurrence the results were far less favorable, with only 2 (9%) of the tumors rendered operable. Only four of the nine patients with operable disease after treatment underwent surgery. This reflects the generally poor condition of this group of elderly patients, and is also suggestive, we believe, of a less aggressive attitude to extensive surgery in earlier years. In spite of a high response rate, median survival was low. Of 11 patients treated for primary disease who responded, but were not operated upon, median survival was 7 months, and in the recurrent group median survival for responders was 7 months. The reason for these disappointing results may be that the total irradiation dose in our material was below 50 Gy.

Thomas et al. (12), using a combination regimen of 5-fluorouracil with or without mitomycin-C and radiation, showed that only 2 of 6 patients with recurrent disease who received less than 50 Gy achieved local control in the vulva, whereas 5 of 7 who received more than 50 Gy achieved local control. The dose and fractionation used in

our series would probably not have been used today. At the start of this study it was thought that the total irradiation dose had to be reduced when bleomycin was added to the treatment, because bleomycin could only be given in a restricted number of fractions. Radiotherapy was also given in a smaller number of fractions compared to standard therapy.

The morbidity in our series was low, and increasing the radiation dose might have improved the results without unacceptable side-effects. Since the start of our study, reports have questioned the use of bleomycin as a radiosensitizer. Vermund et al. (13) reported no increase in regional tumor control when bleomycin was added to radiation therapy for the treatment of squamous cell carcinoma of the upper aerodigestive tract. The morbidity and complication rates were, however, significantly increased.

In general, the optimal fractionation for preoperative radiotherapy is not fully known. The strategy of reducing tumor volume will probably warrant a carefully fractionated high dose. Other mechanisms, e.g., vitality of preoperatively disseminated cells, may be equally well influenced by larger fractions. In transitional cell T2 bladder cancer, 4 Gy × 4 seems as effective in terms of survival as 2 Gy × 23 (14). The relapse pattern in these patients indicates that therapy does not sufficiently influence the local control, and distant metastases do not seem to be essential for the situation of these patients. Therefore we believe that more conventional fractionation schemes, aiming at rather high doses are indicated (15).

Several combination regimens of chemotherapy and radiotherapy for the treatment of squamous cell carcinoma of the vulva have been reported in recent years. Concomitant 5-FU and irradiation with or without mitomycin-C have been used with success by Levin et al. (16) and Thomas et al. (12). However, Whitaker et al. (17) obtained less favorable results when they used the same regimen to treat patients with more advanced disease. Promising results were reported by Berek et al. (18) with concurrent cisplatin/5-FU-radiotherapy. Out of 12 patients treated for primary disease (8 FIGO 3 and 4 FIGO 4), eight showed a complete response. Three patients with PR and one with SD underwent surgery. Ten of the patients were alive and free of disease with a median follow-up of 37 months (range 7–60 months).

However, the results achieved with different treatment regimens are not always comparable, as the term 'advanced disease' may include operable as well as inoperable tumors. In the series of twelve patients reported by Berek et al. (18), 33% had fixed tumors (4 T4) compared to 65% (5 T4, 8 N3) in our group of 20 patients treated for primary disease.

The data from Berek et al. (18) are nonetheless interesting and promising, and support the use of concomitant chemotherapy and radiotherpay to treat advanced squamous cell carcinoma of the vulva.

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