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CARCINOMA OF THE PENIS

Treatment by surgery or combined bleomycin and radiation therapy

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Forty-four patients with squamous cell carcinoma of the penis stage T1–T2, N0 were either treated surgically (n = 19) or with a combination of irradiation and bleomycin (n = 25). The overall actuarial survival rate was 80% at 3 years, 77% at 5 years and 60% at 10 years. The result of irradiation treatment combined with bleomycin was in stage N0 equivalent to that of surgical therapy. The non-surgical treatment had the advantage of preserved sexual ability.

Cancer of penis is a rare type of tumor. In Sweden it accounts for only 0.3% of male cancers with an annual incidence of 1.3/100 000 in the male population (1). Surgery has traditionally been the main form of treatment. Partial amputation or total penectomy leads, however, to functional disability and to psychological distress and therefore radiation therapy combined with bleomycin has been the primary mode of treatment at our hospital ever since 1975. In order to assess the treatment results we have reviewed all the patients with cancer of the penis stage T1–T2, N0 treated at our hospital since 1966.

Material and Methods

A series of 44 patients with squamous cell carcinoma of the penis, stage T1–T2, N0 was treated at the University Hospital of Umeå in 1966–1984. The median age of the patients was 60 years (range 31–83) at the time of diagnosis. Ten patients (23%) were in the age group 31–50 years. Duration of symptoms (tumor, bleeding, balanitis and dysuria) before diagnosis ranged from 1 to 60 months with a mean of 11 months. Evaluation of the patients included physical examination, fine-needle biopsy of inguinal nodes if palpable and chest x-ray. The local findings were ulceration in 17 cases, palpable tumor in 24 cases and both ulceration and tumor in 3 cases. In 21 cases the tumor was localized to the glans, in 3 cases to the prepuce and in 20 cases both the glans and the prepuce were involved. The classification system recommended by the UICC and the WHO grading system were used in categorization of the tumors (2). The T-category and grade of the tumors treated by either surgery or radiation therapy is presented in the Table. None of the patients had distant metastases on admission.

Initial treatment of the primary tumor. Until 1975 surgery was the main form of treatment of penile cancer. Thereafter radiation therapy in combination with bleomycin was the dominating treatment. This combination therapy was introduced by Edsmyr et al. (3, 4). Five patients were treated by surgery after 1975 because of high age. Among the surgically-treated patients, 5 underwent local excision for very small T1 tumors and 14 were treated

Table

The distribution according to T-category and grade (G) in 44 patients

Grade	Surgery		Radiotherapy		Total
	T1	T2	T1	T2	
G1	8	3	10	4	25
G2	3	4	4	5	16
G3	0	1	2	0	3
Total	11	8	16	9	44

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with partial amputation. Radiation therapy to the whole penis was given to 25 patients with ^{60}Co-beam (SSD 60 cm) or 4 MV x-rays from a linear accelerator (SSD 80 cm). Twenty-one patients were circumcized prior to the radiation therapy. During irradiation the penis was held by a plastic device which also served as a bolus to ensure a homogenous dose distribution. Irradiation was given from 2 opposed portals with a daily dose of 1.8 Gy, 5 times per week up to a total dose of 56–58 Gy over a period of 6 weeks corresponding to a CRE value of about 17.3 (5). The patients received 2.5 mg (n = 13) or 5.0 mg (n = 12) of bleomycin i.m., 1 h before each treatment. The total dose of bleomycin was 70–140 mg.

Initial treatment of inguinal nodes. In two surgically treated patients bilateral inguinal lymphadenectomy was performed and in 7 patients radiation therapy was given after surgery to the inguinal regions with a dose of about 55 Gy prophylactically. In the primarily irradiated group inguinal irradiation was given to 2 patients.

Results

The actuarial survival rate of the patients was 80% at 3 years, 77% at 5 years and 60% at 10 years. All the patients have been followed for more than 8 years or until death. No patient has been lost to follow-up. Duration of the symptoms did not differ between the two groups (mean duration 10.9 versus 11.2 months). The actuarial survival of T1–2 N0 patients treated by surgery (n = 19) and radiation (n = 25) respectively is presented in Figs 1 and 2.

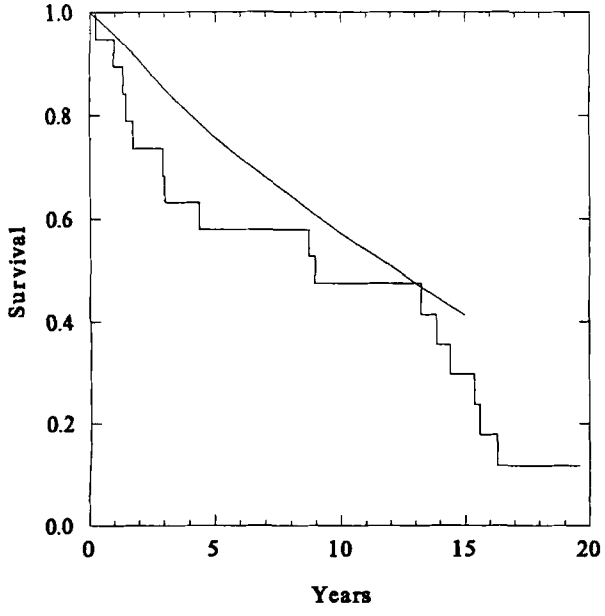

Fig. 1. Uncorrected actuarial survival of 19 surgically treated patients. The survival of an age-matched general male population is indicated.

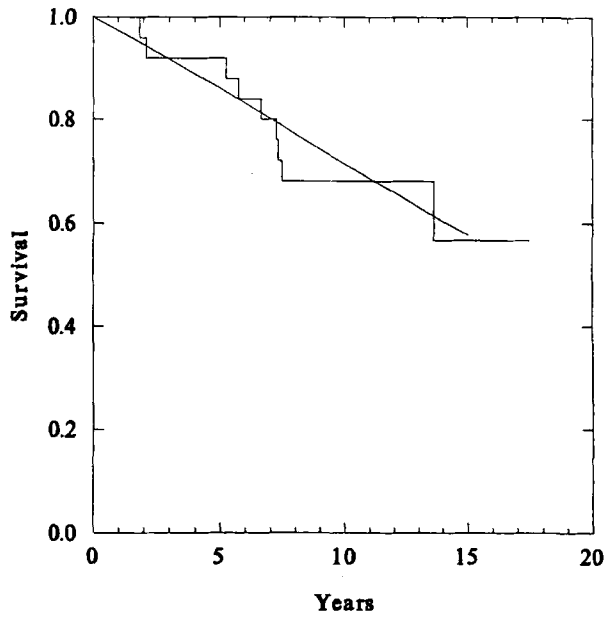

Fig. 2. Uncorrected actuarial survival of 25 patients treated with radiotherapy. The survival of an age-matched general male population is indicated.

The survival was poorer in the surgically treated group but only 2 patients died from penile cancer, 1 patient with inguinal metastases after about 1 year and 1 patient with inguinal and pulmonary metastases after 3.5 years. No patient died from cancer in the irradiated group of patients with T1–2 N0.

Five patients in the irradiated group had a local recurrence at 5, 8, 12 and 18 months and 4 years respectively after therapy. They were successfully treated by partial amputation. Radiotherapy and bleomycin were well tolerated. The acute reaction involved edema of the penis and a mucocutaneous reaction which healed after 3–6 months. Late reactions were in one case a stricture of the urethral meatus which required repeated meatotomy operations. In a few cases a slight fibrosis and cutaneous teleangiectasia were noted. Patients with sexual activity kept their ability.

Discussion

In different experimental systems it has been demonstrated that the combination of bleomycin and radiation has a synergistic effect (6, 7). Randomized clinical trials comparing radiotherapy and bleomycin with radiotherapy alone have shown increased local tumor control for the combination therapy in squamous cell carcinoma of the head and neck (8, 9).

The response of cultured mammalian cells to bleomycin is characterized by a bi-phasic survival curve with an initial steep slope and a terminal more flat portion, indicating that optimal effect can be reached with low doses of bleomycin (10, 11). Further experimental findings (12)

indicate that bleomycin interacts with postirradiation repair processes and that the best sensitizing effect is obtained at low individual doses of radiation. In combination with radiotherapy, small doses of bleomycin given before each radiation dose may have an advantage over fewer and larger doses as used by Edsmyr et al. (4). Cancer of the penis is a disease most common in the sixth and seventh decade. In this material, 10 patients (23%) were suprisingly young (31–50 years). None of those patients were circumcized and all but one had phimosis. Moreover, 10 of them had possible occupational exposure to carcinogens (oil, solvents and tar, etc.). The importance of lack of penile hygiene for the high incidence of carcinoma of the penis has been discussed elsewhere (13).

No difference in survival of patients with T1–2 N0 tumors was found between those treated by surgery or irradiation. The greater number of intercurrent deaths in the surgery group can be attributed to the higher median age at treatment, 65 versus 55 years of age. The follow-up time was shorter in the radiotherapy-bleomycin group, but still the shortest observation time was 8 years. As metastases use to develop within the first three years (14), the results are encouraging, especially since no functional disability was at hand.

It may be argued that treatment with radiation and bleomycin might not completely extradicate but only postpone the development of the tumor. In our material the longest observation time free from tumor was 17 years. The 5 patients surgically treated for local recurrence of the tumor, had no signs of nodal disease or distant metastases. In the irradiated and bleomycin-treated group no patient has developed nodal disease or distant metastases. Provided a careful follow-up can be achieved, treatment with radiation and bleomycin seems justified and possible local recurrence can be surgically treated.

In the surgically treated group with N0 tumors two patients died from cancer of the penis. As the primary tumor was judged to be microscopically completely resected, this means that those patients already at the time of the surgery had micrometastases. The finding that no patient in the radiation-bleomycin-treated group has developed local or distant metastases, may imply that bleomycin can eliminate possible micrometastases.

To conclude, radiation therapy combined with bleomycin in patients with squamous cell carcinoma of the penis in stage T1–T2, N0, M0 seems to give survival results comparable to those of primary surgery. Moreover, the sexual ability is preserved in the originally sexually active man.

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