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research article

Irradiation of regionally advanced carcinoma of the penis

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Background. *Penile cancer patients with inoperable groin metastases as well as patients with residual or recurrent groin tumours after inguinal lymphadenectomy are frequently considered for radiation treatment.*

Methods. *A retrospective study of 12 patients with regionally advanced penile carcinoma treated with radiotherapy in the period 1995-2003 was done. Acute and chronic treatment-related complications were observed.*

Results. *All patients (8/8) with the tumours palpable at the beginning of radiotherapy and two patients (2/4) with microscopic post-lymphadenectomy tumour residue died from the disease. The death occurred 4–24 months after starting radiotherapy. Median survival was 8 months. Locoregional control could only be achieved in patients irradiated for microscopic post-lymphadenectomy tumour residue (4/4).*

Conclusions. *A timely and accurate diagnosis of regional disease spread and immediate lymphadenectomy are of vital importance. Radiotherapy should be applied soon after surgery as postoperative treatment of regional metastases that are at risk to recur – recurrences following lymphadenectomy could not be salvaged by radiotherapy.*

Key words: penile cancer; advanced disease; radiotherapy

Introduction

Penile cancer is a rare disease. According to the data collected by Cancer Registry of Slovenia, the annual incidence of penile cancer is 0.4-1 per 100,000 males.[1]

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The standard treatment modality in penile cancer is surgery, which involves partial or total penectomy, depending upon the stage of primary tumour.[2] In case of enlarged inguinal nodes or the nodes that are not palpable, but at risk to develop metastases due to the nature of primary tumour, penectomy is often followed by inguinal lymphadenectomy.[2]

Radiotherapy is usually indicated when patients do not wish to have their penis removed.[3-5] However, it is also considered in the patients who have the disease in regionally advanced stage and in whom, ac-

Table 1. Characteristics of 12 patients with regionally advanced carcinoma of the penis at the beginning of treatment/beginning of radiotherapy

Patient No.	Initial stage			Lymphadenectomy	Groin status at the beginning of RT†
	T-stage	Grade	N-stage		
1	2	1	0	yes*	microscopic residual
2	2	2-3	0	yes*	microscopic residual
3	2	1	0	yes*	microscopic residual
4	3	2	2	yes	microscopic residual
5	2	2-3	0	yes*	palpable tumour
6	2	2	2	yes	palpable tumour
7	1	1-2	2	yes	palpable tumour
8		3	3	no	palpable tumour
9		3	3	no	palpable tumour
10	2	2	0	no	palpable tumour
11	2	2	0	no	palpable tumour
12	2	2	3	no	palpable tumour

Legend: * - lymphadenectomy was performed after regional progress of the disease; † - RT=radiotherapy

cording to the urologist's estimates, the tumour is inoperable, or the resection of the enlarged lymph nodes was not radical, or post-lymphadenectomy recurrence is diagnosed. The data on what treatment results can be expected in these patients are very scarce.

In order to assess the efficiency of the radiotherapy of penile cancer in Slovenia we started the study in patients with advanced metastases in inguinal region, who were referred to the radiotherapy at the Institute of Oncology Ljubljana.

Patients and methods

This is a retrospective study of 12 patients with cytologically or histologically confirmed squamous cell carcinoma of the penis treated with radiotherapy in the period 1995-2003. The patients did not have distant metastases, but rather extensive metastatic involvement was observed in the inguinal lymph nodes. The patients' data on the primary stage and histology grade of the disease are shown in Table 1. T-stage of the patients 8 and 9 was not determined because, in these patients, penectomy was not performed.

In 6 patients, enlarged inguinal nodes were observed immediately at diagnosis. In others, the enlargement was observed later on; in 4 patients (patients 1, 2, 10, and 11), the nodes were enlarged due to post-penectomy recurrence and surveillance policy, in one (patient 5), the enlargement was observed after prophylactic lymphadenectomy, and in one (patient 3), after sentinel lymph node dissection. In 8 patients (Table 1), radiotherapy was indicated because of palpable inguinal tumours which were diagnosed either as inoperable infiltrations in the nodes in 5 patients (patients 8-12) or as inoperable post-lymphadenectomy locoregional recurrence in 3 (patients 5-7). Microscopic tumour residue detected after lymphadenectomy in 4 patients was also an indication to apply radiotherapy. The microscopic residue was defined as extran-

Table 2. Radiotherapy treatment characteristics of 12 patients with regionally advanced carcinoma of the penis

Patient No.	TD bioequivalent doses for $\alpha/\beta = 10$ (Gy)		
	Inguinal region	Pelvic region	Pubic region
1	50	50	50
2	52		52
3	50	50	50
4	50	50	50
5	58	41	46
6	66	46	50
7	68	47	60
8	52		52
9	44		44
10	25		
11	44		26
12	24	24	24

odal tumour involvement that was, in all 4 patients, accompanied with metastases in several nodes.

In 9 patients, radiotherapy was planned as radical treatment, whereas in 3 patients (patients 10, 11, and 12), radiotherapy was planned to have palliative effect because of the extensiveness of groin tumours. All patients who received palliative radiotherapy and 3 patients who were treated with radical radiotherapy were irradiated by Co^{60} unit, using a single anterior field technique, with a dose determined at a depth of 4-5 cm and the field covering both inguinal regions and pubic area. The remaining 6 patients treated with radical radiotherapy were irradiated by two opposite field technique, with the larger anterior field covering also the lateral part, smaller posterior field limited to pelvic region, and two additional electron fields to boost the irradiation dose to the inguinal region. In all cases, 2-D treatment planning and standard dose fractionations were used – radical radiotherapy was performed at a dose range of 2–2.5 Gy and palliative at 2.5–5 Gy per fraction. Bioequivalent total doses for $\alpha/\beta = 10$ are given in Table 2. Patient 9 was concomitantly treated with chemotherapy and received 2 cycles with cisplatin (100 mg/m^2), methotrexate (40 mg/m^2) and bleomycin-C (10 mg/m^2).

Considering the nature of the present study, acute treatment-related complications were evaluated on the basis of most pronounced problems, while the evaluation of chronic complications was limited to the patients in whom locoregional control of the disease was obtained.

Results

All patients (8/8) with the tumours that were palpable at the beginning of radiotherapy died from the advanced disease, and so did also the two patients (2/4) with microscopic post-lymphadenectomy tumour residue who were referred to radiotherapy (Table 3). The death occurred 4–24

Table 3. Results of treatment of 12 patients with regionally advanced carcinoma of the penis

Patient No.	Local complete remission	Months of follow-up	Status
1	yes	10	dead of disease
2	yes	24	dead of disease
3	yes	43	dead without disease
4	yes	55	no evidence of disease
5	no	17	dead of disease
6	no	16	dead of disease
7	no	8	dead of disease
8	no	8	dead of disease
9	no	10	dead of disease
10	no	6	dead of disease
11	no	4	dead of disease
12	no	4	dead of disease

months after starting radiotherapy. Median survival of these patients was 8 months. Distant metastases were detected in 7/12 patients; in 6/7 patients, the first symptom of disease spread were enlarged retroperitoneal and mediastinal lymph nodes. In patient 3, who died 43 months after starting radiotherapy, the cause of death was carcinoma of the sigmoid colon. Patient 4 was alive and with no evidence of disease 55 months after radiotherapy.

In none of 8 patients who had palpable tumours in the inguinal region at the beginning of radiotherapy, complete locoregional control was obtained. Of these 8 patients, 5 were treated with radical radiotherapy.

In 3 patients with post-lymphadenectomy recurrence, deep ulcerations with cytologically confirmed tumour residue in necrotic margins developed after radiotherapy on the sites of inguinal tumours. Further progress of the disease in the field margins was observed in 2 patients who both developed lymphangitis carcinomatosa prior to irradiation – patient 6 on the skin of partly shielded penis residue and patient 5 on the skin of the scrotum and of the thigh. In the patients in whom radiotherapy was indicated for the treatment of microscopic post-lymphadenectomy tumour residue, locoregional progress of the disease was not assessed.

Pronounced acute toxicity was limited to confluent radiodermatitis that developed in the patients irradiated with the doses over 50 Gy. In patient 9, who was treated with concurrent chemoradiotherapy, radiodermatitis was so severe that irradiation had to be discontinued.

In the patients in whom locoregional control of the disease was obtained, the only chronic treatment-related complications were edematous penis and scrotum and atrophic skin in the inguinal folds.

Discussion

In the patients with penile carcinoma, the regional lymph node status proved to be an

independent prognostic factor.[4] Prognosis of the patients with the regional disease depends upon the extensiveness of metastases. If metastatic spread in an early stage is detected immediately upon prophylactic or therapeutic lymphadenectomy, more than three quarters of patients can survive,[6-8] whereas in case of the metastatic spread in an advanced stage with bilateral nodal infiltration as well as extranodal tumour extension, less than 12% of patients may survive.[9] A similar observation was pursued in our study in which only 2/12 patients survived with regionally advanced disease after radiotherapy. Bilateral or clinically fixed nodes with extranodal extension at lymphadenectomy (when it was applied) were present in all our patients. A quick systemic progress of the disease observed only a few months after the completed irradiation in 7/12 patients from our study may speak in favour of the presence of distant metastases that remained undetected at the regional disease stage.

Upon the disease spread in the inguinal region (groin tumours), it is hard to obtain and keep local control of the disease.[4,10] The patients with recurrence or palpable post-lymphadenectomy tumour residue may be as problematic as the patients with inoperable metastases. In any of these patients from our study, local control was not achieved, and they all developed deep ulcerations after the completed radiotherapy; in one of them, even the perforation of femoral artery occurred. This may further support the view that the limited tolerance of healthy tissue following the inguinal lymphadenectomy does not allow the application of doses that would assure local control. Therefore, an inguinal tumour that is still palpable after inguinal lymphadenectomy or detected as a recurrence is not only an indication of extremely bad prognosis, but also of very poor quality of the patient's life due to further local complications.

On the other hand, radiotherapy may be most effective in microscopic disease control, at least in terms of local control.[6] However, the results seem to be somehow conflicting. Mazeron reported uncontrolled metastatic nodes in 4/5 patients after selective dissection of enlarged nodes (2 patients) or groin dissection (3 patients) and postoperative inguinal irradiation with Co^{60} and electrons applied in 4/5 patients.[5] Four patients from our study may well be a proof of the efficiency and of acceptable chronic toxicity of postoperative irradiation. All four, though they were treated with macroscopic radical lymphadenectomy, were also irradiated postoperatively because of extranodal tumour extension and numerous positive nodes. In all 4 patients, a stable local control was obtained. Radiotherapy proved to be successful also in terms of treatment-related complications which were, in all patients, within the limits of somewhat more pronounced fibrosis of the inguinal region. The efficiency of postoperative radiotherapy is an important aspect that needs particular consideration because the incidence of locoregional recurrences following radical therapeutic lymphadenectomy seem to be rather high; in the study by D'Ancona, it was reported to be 37%.[11]

In conclusion, a timely and accurate diagnosis of regional disease spread and immediate lymphadenectomy are both of vital importance for the patients with penile cancer.[7,12] In order to assure the patients a proper quality of life and survival, particular care should be taken that the regional control of the disease is obtained by primary treatment. Due to limited number of patients it would be invalid to draw firm conclusions; nevertheless, we believe that radiotherapy should be applied soon after surgery as postoperative treatment of regional metastases that are at risk to recur. Recurrences following lymphadenectomy could not be salvaged by radiotherapy.

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