Neoadjuvant Chemotherapy Followed by Aggressive Surgical Consolidation for Metastatic Penile Squamous Cell Carcinoma

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Purpose: Combination chemotherapy for advanced penile cancer can produce partial response rates of up to 64%. Complete responses are rare, suggesting a need for adjunct therapies to facilitate cure. We evaluated patients with metastases who underwent surgical consolidation after responding to chemotherapy.

Materials and Methods: We reviewed the records of 59 patients with advanced penile carcinoma treated from 1985 to 2000 and identified 10 treated with surgical consolidation after demonstrating a stable, partial or complete response to chemotherapy. Presenting tumor burden included pelvic and inguinal metastases. Surgical outcomes and survival were assessed.

Results: After chemotherapy 4 patients had a complete response, 1 had a partial response and 5 had stable disease. Three major perioperative complications, including postoperative bleeding, an episode of acute renal failure and deep venous thrombosis in 1 patient each, and 4 minor complications, including skin breakdowns in 3 and wound seroma in 1, occurred. Three cases were rendered pN0. All 3 patients received ifosfamide, paclitaxel and cisplatin chemotherapy. Seven patients had 3 or fewer metastatic lymph nodes following surgery, of whom 4 showed no disease and 3 died. All 3 patients with greater than 3 metastatic lymph nodes died. For all patients the 5-year actuarial survival rate was 40% with a median survival of 26 months. Patients with 3 or fewer and greater than 3 positive nodes had a median survival of 48 and 23 months, respectively ($p = 0.116$).

Conclusions: Select patients with metastatic penile cancer that shows disease stabilization or a response to chemotherapy should be considered for surgical consolidation to extend survival.

Key Words: penis; penile neoplasms; carcinoma, squamous cell; drug therapy; lymph nodes

Carcinoma of the penis is a rare disease that accounts for less than 1% of malignant tumors in males in the Western hemisphere. Standard therapy for SCC of the penis with regional metastases is inguinal and possibly pelvic LND. The presence and extent of LN metastases dictates patient survival. Previous reports suggested that surgery alone is unlikely to cure disease that shows microscopic involvement of more than 2 lymph nodes, involvement of pelvic LNs or extranodal extension of cancer.[1–3] Depending on the extent of nodal involvement surgical treatment can yield 5-year survival rates of 0% to 76%.[1–6]

Several chemotherapy agents have been used for metastatic penile cancer, of which the most common is BMP. When used individually, bleomycin, methotrexate and cisplatin each produces a response rate of approximately 20%.[7–13] However, combination regimens have yielded objective responses in 25% to 72% of cases.[14–16] Unfortunately CRs remain rare with most responding patients achieving a partial response of short duration.[14–16] A few recent reports suggested that neoadjuvant chemotherapy followed by consolidating treatment (radiation or surgery) may maximize survival in patients with poor prognostic variables, ie large volume metastases.[17–19] We report our experience with surgical consolidation for a select group of patients with clinically evident or pathologically proven LN involvement who initially demonstrated stable disease or an objective response to chemotherapy.

MATERIALS AND METHODS

The records of 59 patients who were treated for SCC of the penis from 1985 to 2000 were reviewed to identify those with regionally advanced or metastatic disease who responded or remained stable after chemotherapy and who were subsequently treated with consolidative surgery. In all patients metastases were diagnosed by fine needle aspiration, prior limited inguinal LND and/or obvious bulky metastases on CT before induction chemotherapy. Disease extent was determined using CT of the abdomen and pelvis as well as chest imaging with x-ray or CT. The cohort included patients referred after experiencing disease recurrence after previous surgical therapy (including limited LND) elsewhere. Patients with fixed pelvic masses or inguinal masses showing femoral artery encasement were excluded from analysis. Ten patients met these criteria.

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TABLE 1. *Patient characteristics, chemotherapy regimens and outcomes*

Pt No.—Age at Diagnosis	Clinical Node Size	Prechemotherapy TNM Stage	Chemotherapy Regimen	Chemotherapy Response	No. Pos Nodes	Survival (mos)	Status
1—63	3	TxN3M0	ITP	CR	8	30	DOD
2—86	4.5	T3N1M0	ITP	CR	0	73	NED
3—76	6	T3N3M0	ITP	CR	0	21	Dead, unknown causes
4—75	4	T1N3M0	ITP	Stable	7	23	DOD
5—56	4	TxN2M0	PC	PR	1	50	NED
6—56	12	T3N3M1	BMP	Stable	3	7	DOD
7—41	5	TxN1M0	PC	Stable	3	84	NED
8—44	15	T1N3M0	ITP	CR	0	48	NED
9—73	6	T2N3M0	BMP	Stable	8	3	Dead, failure to thrive
10—45	5	T1N3M0	BMP	Stable	2	7	DOD

Induction chemotherapy regimens consisted of ITP, BMP and PC. Five patients received the ITP regimen, in which cycles were administered during 21 days for a total of 4 or 5 cycles. On day 1 175 mg/m^2 paclitaxel were administered intravenously for 5 days. On days 1 to 3, 1.2 gm/m^2 ifosfamide and 20 mg/m^2 cisplatin were given intravenously. Three patients received the BMP regimen, in which cycles were administered during 28 days for a total of 2 to 9 cycles. On days 1, 15 and 22, 200 mg/m^2 methotrexate were administered intravenously. On days 2 through 6 patients were given 10 mg/m^2 bleomycin daily by intravenous infusion for a total of 50 mg/m^2 as well as 20 to 30 mg/m^2 cisplatin intravenously daily for a total of 5 days. Two patients were given the PC regimen for a total of 4 cycles. On day 1 paclitaxel was given intravenously at a dose of 80 to 200 mg/m^2 and carboplatin was given at a dose of AUC 6 (mg $\times$ minutes)/ml.

Chemotherapy related toxicity was graded according to National Cancer Institute Common Toxicity Criteria, version 3.0. For study purposes toxicity of grades III or higher was reported. Chemotherapy courses were repeated pending adequate hematological recovery (granulocyte count at least 1,000/mm^3 and platelet count at least 75,000/mm^3) and no grade III or IV toxicity. Creatinine and creatinine clearance were monitored closely during chemotherapy administration and doses were adjusted accordingly.

Followup CT after chemotherapy showing no adenopathy larger than 1.0 cm was considered to represent a CR. Residual adenopathy greater than 1.0 cm was considered to indicate a PR if disease met Response Evaluation Criteria in Solid Tumors. A 20% or more increase in lesion size, or the appearance of new lesions was deemed progressive disease. All other responses were considered stable disease.

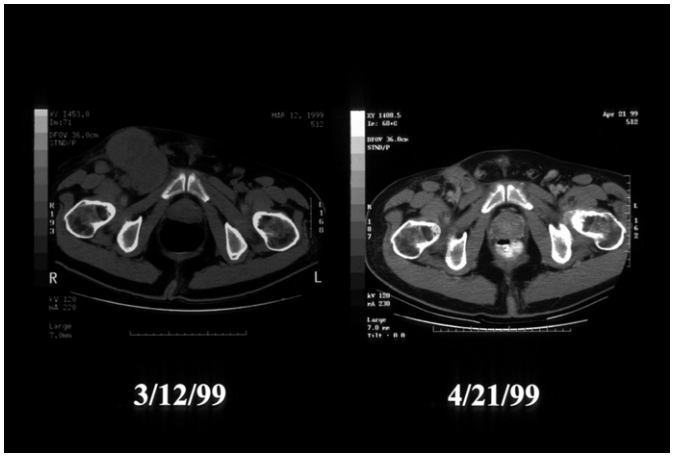
After chemotherapy all patients underwent extensive LND in an attempt to remove all residual disease, as reported previously.[18] This LND included the possibility of resecting the inguinal ligament, the inferior aspect of the rectus abdominis or external and internal oblique muscles, the spermatic cord and ipsilateral testicle, and segments of the femoral artery and vein with subsequent patch or bypass grafting. Ipsilateral pelvic LND was also performed on the side of positive inguinal LNs or radiographic evidence of pelvic lymphadenopathy. Plastic surgery consultation was obtained for wound coverage, including the insertion of monofilament polypropylene mesh for abdominal wall defects, and myocutaneous flaps of the sartorius, rectus abdominis, serratus anterior and latissimus dorsi muscles.

Information on patient age, date of diagnosis, clinical stage, primary treatment, neoadjuvant chemotherapy agents, previous surgical procedures, total number of LNs removed, and size and number of metastatic LNs was obtained from patient medical records. Disease was restaged for this analysis according to the 1997 TNM staging system. Minor and major complications after surgery were noted. Survival variables were calculated from the date of consolidative surgery and plotted according to the Kaplan-Meier method. Comparisons between groups of patients were made using Student's t test.

RESULTS

Ten patients with metastatic penile carcinoma were identified who underwent surgical consolidation after demonstrating at least stable disease after chemotherapy (table 1). Median patient age was 56 years (range 41 to 86). Seven patients presented with unilateral lymphadenopathy and 3 had bilateral lymphadenopathy. Median nodal size was 5 cm (range 3 to 15).

Systemic chemotherapy was tolerated well by 7 of the 10 patients, while 3 experienced grade III nonhematological toxicity, including 1 episode each of bleomycin toxicity, acute renal failure and deep venous thrombosis. Four of the 10 patients achieved a CR, 1 achieved a PR and 5 had stable disease after chemotherapy. Responses tended to occur rapidly during treatment, often with substantial improvement after the first 1 or 2 chemotherapy courses. The figure represents a patient who achieved a PR after 6 weeks of combination ifosfamide, paclitaxel and cisplatin chemotherapy.



Male patient with metastatic involvement of right inguinal LNs achieved PR after 6 weeks (2 cycles) of combination ITP chemotherapy. After additional 2 therapy cycles disease was pT0 at surgery (data not shown).