Original Study

Clinical Outcomes of Perioperative Chemotherapy in Patients With Locally Advanced Penile Squamous-Cell Carcinoma: Results of a Multicenter Analysis

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Abstract

Patients with locally advanced penile squamous-cell carcinoma have a poor prognosis. No difference in survival was noted when using chemotherapy before or after surgery. Uncertainties persist regarding the optimal management of these patients, and new treatments are urgently required, particularly for patients at highest risk, with bilateral and/or pelvic lymph node involvement.

Background: The prognosis of patients with locally advanced penile squamous-cell carcinoma is primarily related to the extent of lymph node metastases. Surgery alone yields suboptimal results, and there is a paucity of data on these patients' outcomes. **Patients and Methods:** This retrospective study evaluated patients who received neoadjuvant or adjuvant chemotherapy from 1990 onward at 12 centers. Cox models were used to investigate prognostic factors for relapse-free survival and overall survival (OS). **Results:** Among the 201 included patients, 39 (19.4%) had disease of T3-4 and N0 clinical stage; the remaining patients had clinical lymph node involvement (cN+). Ninety-four patients received neoadjuvant chemotherapy (group 1), 78 received adjuvant chemotherapy (group 2), and 21 received both (group 3). Eight patients for whom the timing of perioperative chemotherapy administration was unavailable were included in the Cox analyses. Forty-three patients (21.4%) received chemoradiation. Multivariate analysis for OS (n = 172) revealed bilateral disease (P = .035) as a negative prognostic factor, while pelvic cN+ tended to be nonsignificantly associated with decreased OS (P = .076). One-year relapse-free survival was 35.6%, 60.6%, and 45.1% in the 3 groups, respectively. One-year OS was 61.3%, 82.2%, and 75%, respectively. No significant differences were seen on univariable analyses for OS between the groups (P = .45). Platinum type of chemotherapy and

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chemoradiation were not significantly associated with any outcome analyzed. **Conclusion:** Benchmark survival estimates for patients receiving perioperative chemotherapy for locally advanced penile squamous-cell carcinoma have been provided, with no substantial differences observed between neoadjuvant and adjuvant administration. This analysis may result in improved patient information, although prospective studies are warranted.

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Introduction

Penile squamous-cell carcinoma (PSCC) is a very rare tumor, and prognosis more frequently depends on locoregional spread than the development of distant metastases.[1] For patients with locally advanced disease, ie, regional lymph node involvement or unresectable bulky primary tumors, clinical guidelines and trial designs recommend induction chemotherapy, possibly before radical surgery.[2,3] Outcomes are poor for patients who experience relapse after surgery or who have extensive involvement of the locoregional lymph nodes (ie, involvement of fixed inguinal lymph nodes or pelvic lymph nodes), and new therapeutic modalities are needed for such patients.

For advanced PSCC, single therapeutic modalities like inguinal lymph node dissection, with or without the extension to pelvic lymph nodes, systemic treatments, or radiotherapy, do not significantly change the limited survival possibilities in the long term for these patients; thus, curing advanced disease often requires a multimodal approach.[4,5] Multiple neoadjuvant chemotherapies have shown moderate activity: the highest reported objective response rates (ORR) are approximately 50%, but relapses occur in the majority of cases, and long-term remission is rare.

Importantly, the optimal timing of chemotherapy and radiotherapy administration with respect to lymph node dissection is unclear, and the results of multiple small studies are conflicting. Usually neoadjuvant therapy is the preferred treatment approach because tumor debulking can facilitate radical surgery and allow for assessment of the pathologic response to chemotherapy. Pathologic complete response (CR) is a surrogate for overall survival (OS) in these patients and is a reliable end point for phase 2 trials.[6] Although the efficacy of adjuvant chemotherapy has only been evaluated in small studies that used obsolete chemotherapy regimens, that treatment approach may benefit select high-risk patients, such as those with pathologically involved pelvic lymph nodes.[7,8] Many of the uncertainties regarding treatment for advanced PSCC described above may be clarified by the results of an ongoing prospective international study (ie, the International Penile Advanced Cancer Trial, InPACT, NCT02305654). That study aims to evaluate the impact of neoadjuvant chemotherapy alone or in conjunction with radiotherapy in patients with lymph node–positive disease. However, until those results are published, information can only be obtained from retrospective analyses. Therefore, the present study evaluated the outcomes of patients receiving perioperative chemotherapy to identify clinical baseline prognostic factors that can be used when determining what multimodal treatment to implement. It is expected that these objectives will provide physicians with the background information necessary to improve patient counseling and treatment.

Patients and Methods

Patient Population

Data were collected from 12 centers in Europe, the United States, and Canada. After the study was approved by the ethics committee and internal review board of each participating center, uniform anonymized data, including baseline characteristics, pathology information, treatments, and chemotherapy regimens, were collected using an Excel spreadsheet. The criteria for case collection were histologically proven PSCC (histologic variants of squamous-cell carcinoma were allowed) and one of the following: clinical evidence of advanced primary tumor (eg, T3-4 N0) and/or clinically involved regional lymph nodes. We relied on the 2009 tumor, node, metastasis classification system,[9] which defines N1 stage as the presence of palpable mobile unilateral inguinal lymph node, N2 stage when mobile multiple unilateral or bilateral inguinal lymph nodes are present, and N3 stage when fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral, are found.

Administration of at least 2 cycles of any chemotherapy course in either a neoadjuvant or adjuvant setting from 1990 onward was required. Prior administration of chemotherapy (ie, vinblastine, bleomycin, and methotrexate regimens) for noninfiltrating PSCC was allowed.[10] The administration of any targeted therapy combined with chemotherapy was allowed. Concomitant or sequential delivery of radiotherapy to the regional lymph nodes was also allowed. Patients with confirmed systemic metastatic disease were not included. All statistical analyses were conducted externally by a senior statistician (G.P.).

Statistical Analyses

Patient, disease, and outcome characteristics were summarized using descriptive statistics with frequencies and percentages used for categorical variables and medians and interquartile ranges used for continuous variables.

The primary objective was to summarize the outcomes of patients who had received any neoadjuvant or adjuvant chemotherapy in addition to radical surgical resection. The secondary objective was to investigate the effect of clinical baseline (ie, presurgical) factors on the prognosis of patients who received surgery and systemic therapy as a result of the clinical evidence of lymph node metastases, irrespective of the timing of the systemic therapy (ie, before or after surgery). OS was the primary end point and was defined as the period of survival from the date of the first administration of chemotherapy.

The Kaplan-Meier method was used to estimate time-to-event outcomes. Cox proportional hazards regression was used to investigate potential prognostic factors of OS and relapse-free survival (RFS). Because clinical data were missing in many cases—the result