EDITORIAL

Adjuvant chemotherapy in penile cancer? Raising more questions than answers

Squamous cell carcinoma of the penis is a rare malignant tumor. Its incidence in North America and Europe has been reported as 0.4 to 0.6% of all neoplasias.1 Unfortunately in Mexico, and according to the latest register of malignant tumors from the year 2011, there is no reliable statistical information on penile cancer and it does not appear among the documented tumors. Therefore, and because only a few cases are systematically published and evaluated, there is great heterogeneity in local disease management, especially in regard to systemic chemotherapy treatment of lymph node and metastatic disease.

The extension of lymph node metastases is an important prognostic factor in penile cancer, and pelvic lymph node disease in particular has a poor long-term survival prognosis.2 One study showed that extracapsular extension, metastasis in 3 or more lymph nodes, or a lymph node lesion greater than 3 cm are predictors of metastasis in the pelvic lymph nodes.3 Five-year survival was 33.2% in patients with positive pelvic lymph nodes, compared with 71% in those with negative lymph nodes. Management with adjuvant chemotherapy and its results are largely unknown, based only on a few studies, with a small sample and in a single hospital center. In addition, no ideal regimen for these patients has been established.4-6 Therefore, the aim of the study reviewed here was to show improvement in overall survival through the use of adjuvant chemotherapy for patients presenting with positive pelvic lymph nodes.

The study referred to in this editorial was a retrospective review by Sharma et al. that identified 141 patients that underwent inguinal and pelvic lymph node dissection due to squamous cell carcinoma, with positive pelvic lymph nodes and no distant metastasis. It included patients seen at 4 referral centers over a 35-year period. Fifty-seven patients that received chemotherapy before surgery or in the presence of recurrence were excluded from the study.

Pelvic lymphadenectomy was indicated for patients that presented with extracapsular invasion or more than 2 positive inguinal lymph nodes. In regard to technique, it should be mentioned that before 2008 the criteria for carrying out pelvic lymph node dissection varied importantly. In relation to extension, at least at all the centers during the study time frame, the obturator lymph nodes and internal and external iliac lymph nodes were extracted.

The adjuvant chemotherapy regimens employed were those based on platinum and those not based on platinum. The administration of these regimens was supported by previous reports on their effectiveness in penile cancer. The choice of regimen depended on the center. Before 1994 the most common regimen was bleomycin-vincristine-methotrexate (VBM) and after 1994 platinum-based regimens were the most widely used.

The patients that had positive pelvic lymph nodes presented with a clinical stage of T2 or higher. During follow-up, 46% of the patients had recurrence. The most common was local recurrence in 51%, followed by regional lymph nodes in 44%, and then distant disease in 5%. The platinum-based chemotherapy regimen was used in 78% of the patients, mean follow-up time was 12.1 months, and the estimated mean overall survival was 13.9 months. Improvement in overall survival was 11.6 months with adjuvant chemotherapy vs. 10.1 months with surveillance only. The multivariate analysis found that chemotherapy was an independent factor for the increase in overall survival. It should be mentioned that the patients that received adjuvant chemotherapy were younger, had fewer comorbidities, and presented with less aggressive disease than those that were under surveillance.7-10

In relation to previous results, we can reach certain conclusions: patients with penile cancer with positive pelvic lymph nodes will benefit not only from aggressive surgical treatment, but also from adjuvant chemotherapy regimens. Even though there is still no ideal regimen, everything seems to indicate that the platinum-based regimens could be the option. However, studies with adequate methodologies are needed in order to form a solid opinion, despite the fact that the 2015 updated guidelines of the
European Association of Urology on penile cancer recommend adjuvant chemotherapy for N2 and N3 patients. This recommendation has been carried out in small nonrandomized studies and most are conducted on patients with positive inguinal lymph nodes.

Young patients with fewer comorbidities will benefit more from the adjuvant chemotherapy regimens, most likely because they will better tolerate the adverse effects. It is doubtful that patients with comorbidities or a poor functional state will benefit. The benefits of neoadjuvant chemotherapy for patients with pelvic lymph nodes is currently a subject of debate, based on the extrapolation of neoadjuvant results in patients with initially unresectable N3 disease that was downstaged to resectable disease. The strongest predictor of 5-year survival was the response to the neoadjuvant chemotherapy, together with consolidative lymphadenectomy.11-13 Finally, the number or density of resected inguinal and pelvic lymph nodes was available in said study, but previous studies did not include the importance of the number of lymph nodes obtained during lymphadenectomy. Likewise, we have no information as to whether there is a difference in survival in relation to pelvic lymphadenectomy extension.14

In conclusion, we believe that patients with penile cancer will benefit from aggressive surgical management, together with adjuvant chemotherapy for those that present with risk factors for recurrence, such as the patients presenting with N2 and N3 disease, to be able to increase their overall survival, especially in young patients with few comorbidities.

References


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