



Cancer of the penis: narrative review of advanced inguinal metastatic disease focusing on optimizing the associations of surgery and chemotherapy

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Background and Objective: Metastatic dissemination of squamous cell carcinoma of the penis is preferentially carried out through the lymph node chain of the inguinal regions, with visceral metastases due to hematogenous dissemination being rare. In this review, we intend to evaluate treatment options for patients who have undergone lymphadenectomy and who are diagnosed with metastatic inguinal lymph nodes.

Methods: The review is focused on surgery and neoadjuvant/adjuvant chemotherapy. Research into the latest developments in penile cancer treatment was performed. National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines were consulted, as well as studies searched using PubMed search tools. Titles and abstracts were screened covering one of the following study endpoints: penile cancer, staging, lymphadenectomy, lymph node metastases, palliative surgery, recurrence, neoadjuvant, and adjuvant chemotherapy.

Key Content and Findings: Staging changes according to the eighth edition of the American Joint Committee on Cancer tumor, node and metastasis (AJCC TNM) include changes in regional lymph node staging with pN1 characterized as the presence of 2 or fewer unilateral inguinal metastases without extranodal extension and pN2 with 3 or more unilateral inguinal metastases or bilateral metastases. In clinical practice, non-invasive methods for assessing the presence or absence of inguinal metastases are unreliable.

Conclusions: The survival of patients is closely related to the presence and the extent of metastases to the inguinal region, which constitutes the most important prognostic factor of the disease. Recurrence in the inguinal region carries a poor prognosis. Neoadjuvant chemotherapy allows salvage surgery by transforming irreparable inguinal metastatic lesions into resectable ones. Paclitaxel, ifosfamide and cisplatin (TPI) is the most used neoadjuvant chemotherapy regimen before surgery in patients with positive lymph nodes greater than or equal to 4 cm, fixed or mobile. T4 patients with unresectable tumors can be downstaged after chemotherapy. The combination of 5-fluorouracil (5-FU) with cisplatin was able to generate, in some series, objective responses in up to 66% of patients, allowing salvage surgery. According to NCCN guidelines, studies with adjuvant chemotherapy do not allow definitive conclusions. Patients may benefit from adjuvant chemotherapy when they are at high risk of systemic spread or local recurrence. Palliation should be used for patients with disseminated disease whose prognosis is poor. In selected patients, paclitaxel or cetuximab can be used.

Keywords: Penile cancer; inguinal lymph node disease; surgery; chemotherapy

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Introduction

Background

Penile squamous cell carcinoma is a rare entity whose treatment morbidity often brings physical and mental stigma to patients. It occurs mainly in patients with low socioeconomic status in underdeveloped countries (1). Brazil has one of the highest incidences of penile cancer in the world, representing, in some areas, around 17% of all male malignant neoplasms (2).

Clinical presentation may vary, with ulceration of the foreskin and glans being the most reported symptoms (3,4). In its presentation, the glans appears as the initial site in 48% of the cases, followed by the foreskin (21%), glans and prepuce (9%), coronal sulcus (6%) and penile shaft with less than 2% (5,6). Rare hematogenous dissemination of the disease occurs with invasion of intracorporeal vascular space after penetration of Buck's fascia and tunica albuginea (7,8).

In squamous cell carcinoma of penis (SCCP), the lymphatic route is the main route of dissemination of metastases with hematogenous dissemination rates ranging from 1% to 10% (9-11).

Penile carcinoma has an aggressive and progressive course, with patients dying in less than 2 years after diagnosis of the primary lesion when deprived of treatment. Lethality is due to uncontrollable complications such as chronic infections, sepsis, hemorrhage due to rupture of femoral vessels and systemic dissemination of the disease (9,12,13).

The most important factors for the survival of patients with SCCP are the presence or absence of inguinal metastases. Initially, the first site of metastasis is in the inguinal region, followed by a generally prolonged locoregional phase and later distant metastases (14). Therefore, the route of spread is usually via the inguinal nodes to pelvic nodes and then to distant sites.

Rationale and knowledge gap

Advanced penile cancer defies existing treatments. It is a serious and rare disease with few patients analyzed and randomized in relation to surgical and chemotherapy treatments. Therefore, there is no consensus on the best approach to the disease and on which treatment should be used first.

Objective

The objective of this review is to search the current

literature for the best treatment options for patients undergoing lymphadenectomy with advanced inguinal lymph node disease.

Methods

The review is based on the surgical and chemotherapy treatment of patients with penile cancer metastases to inguinal lymph nodes. Relevant studies on this topic have been included based on the author's expert experience over the last 35 years. PubMed, National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) penile cancer guidelines were used to select the most relevant studies that should include one of the following endpoints: penile cancer, staging, lymphadenectomy, lymph node metastases, palliative surgery, recurrence, neoadjuvant and adjuvant chemotherapy (*Table 1*).

Results

Staging

The most recent penile cancer staging system, tumor, node and metastasis (TNM) used by the American Joint Committee on Cancer (AJCC) has its most recent update (eighth edition) published in 2017 (15). Definitions of primary tumor (T) have changed to include non-invasive carcinoma (Ta) with T1 being described by its location in the penis and the invasion of each site examined. The 8th AJCC-TNM staging system also includes presence of lymphovascular embolization, perineural invasion, and the degree of differentiation into the T1 category, as a prognostic indicator, thus separating T1b from T1a stages. Invasion of the corpus spongiosum was included in stage T2 and invasion of corpora cavernosa in stage T3. This edition also changed the definitions of regional lymph nodes (N), with pN1 defined as 2 or less than 2 unilateral metastases to the inguinal region without extranodal extension and pN2 as 3 or more than 3 unilateral or bilateral metastases. In addition, the AJCC recommends using the World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading system for SCCP, which considers grade 1 as well-differentiated tumor, grade 2 as moderately differentiated tumor, and grade 3 as poorly differentiated tumor or undifferentiated.

Approach of inguinal lymph nodes

The most important prognostic factors for the survival

Table 1 The search strategy summary

Items	Specification
Date of search	August 2022
Databases and other sources searched	PubMed, NCCN and EAU penile cancer guidelines
Search terms used	Penile cancer, staging, lymphadenectomy, lymph node metastases, palliative surgery, recurrence, neoadjuvant, and adjuvant chemotherapy
Timeframe	1962–2022
Inclusion criteria	Discussed treatment modalities with an emphasis on surgery and chemotherapy in penile cancer with inguinal lymph node disease; no language restrictions as long as translation is available
Exclusion criteria	Case reports, studies and articles that did not meet the above criteria
Selection process	Performed by the corresponding author

NCCN, National Comprehensive Cancer Network; EAU, European Association of Urology.

of patients with penile carcinoma are the presence and extent of inguinal metastases (16). Invariably, the first site where metastases occur is the inguinal region. There is a prolonged locoregional phase before the appearance of distant metastases. This justifies performing a prophylactic or therapeutic inguinal lymphadenectomy (ILND) with the intention of curing the patient. However, the ideal time to surgically approach the inguinal region remains controversial.

Evaluation of inguinal lymph nodes

Based on these findings, a series of attempts to identify metastases in inguinal lymph nodes, without submitting patients to unnecessary lymphadenectomies, were launched.

Ultrasonography and color Doppler are useful to evaluate the lymph nodes when they are palpable, due to the presence of abnormalities in their architecture and vascularization (17–21). However, the sensitivity and specificity of this method can sometimes be inadequate (22), except when associated with a fine needle aspiration cytology (FNAC) (18,19,23). The combination of FNAC with ultrasound (US) has a sensitivity of 40% and a specificity of 100% (19,23) showing that this approach can be used in the initial investigation when patients have palpable lymph nodes and are at high risk of lymph node metastases (18). However, only metastases larger than 2 mm can be detected (23). US-guided FNAC is only valuable when positive, as rates of up to 29% of false-negative results have been described (18,24–26). If the clinical suspicion

persists, even when the FNAC is negative, repeated aspirations can be performed (26).

Crawshaw *et al.* (21) performed a prospective study to evaluate the accuracy of dynamic sentinel lymph node biopsy (DSNB) combined with inguinal ultrasonography, with or without FNAB. Occult metastatic lymph nodes have been identified with a negative predictive value of 100% (18,19,21). The method consists of intradermal injection of technetium-99m nanocolloid and patent blue dye around the primary tumor. Next, preoperative lymphoscintigraphy is performed to identify, with a gamma-ray detection transducer, the sentinel lymph node. This is visualized surgically as it has been previously stained by intradermal administration of patent blue dye (18,27). Horenblas *et al.* (28) have favored this method for evaluating regional lymph nodes. Leijte *et al.* (29) obtained a 97% sentinel node detection rate with a 7% false-negative rate with DSNB. The most common cause of false-negative DSNB is the exuberant involvement of the sentinel lymph node by tumor cells, which makes radiotracer uptake impossible (28,30).

When inguinal lymph nodes are not palpable, computed tomography (CT) or magnetic resonance imaging (MRI) has limited ability to detect metastases (18–20,26,28,31). On CT, positive findings were found only in patients with suspicious lymph nodes on clinical examination (24,28). Therefore, CT and MRI are indicated only to assess the size, extent, and location of inguinal lymph nodes, as well as pelvic and retroperitoneal lymph nodes. By these methods it is also possible to assess whether or not there is involvement of large vessels (28). MRI with lymphotropic nanoparticles (LNMRI) is a recent and promising method,

which uses tiny superparamagnetic iron oxide particles (ferumoxtran-10), which are not taken up by malignant lymph nodes. By this method based on lymph node function, it is possible to detect occult metastases smaller than 1 centimeter and, therefore, diagnose patients without palpable inguinal lymph nodes (18,19,28,32). This test had 100% sensitivity and 97% specificity (32). With this method, lymph node metastases measuring 1 mm have been detected in patients with prostate cancer (28,33). Regarding LNMRI, the contrast medium used is not affordable, as ferumoxtran-10 is not approved by the US Food and Drug Administration (FDA) and is no longer available in Europe (19,20). In addition, the interpretation of the result requires careful evaluation by the radiologist.

Diffusion magnetic resonance, widely investigated in cancer patients, is a modality that reveals structural alterations in different tissues (34,35). Thoeny *et al.* (36) studied diffusion MRI associated with LMNRI for the detection of occult metastatic lymph nodes in the analysis of patients with prostate and bladder cancer and considered it an effective and rapid method for this purpose.

A variety of neoplasms can be studied using positron emission tomography (PET) and 18F-fluorodeoxyglucose (FDG). This technique reveals a high sensitivity and specificity to detect metastases and tumor recurrences. This method alone does not provide morphological, only metabolic details. PET combined with CT (PET-CT) allows access to anatomical and functional information (18).

Zhang *et al.* (37) studied 48 patients with penile cancer using FDG-PET/CT. Of these patients, 39 had already undergone CT and 9 underwent MRI. One hundred and fifteen individual lesions were evaluated in 42 patients with a sensitivity of 85% and specificity of 86%. FDG-PET/CT detected more tumors than MRI CT in 33% of patients, allowing treatment to be changed in 57% of cases. Therefore, FDG-PET/CT may be useful to detect metastases in penile cancer and allow a change in the course of treatment.

Using PET-CT for staging patients with SCCP, Scher *et al.* (38) achieved a sensitivity of 89% in detecting metastases in superficial inguinal lymph nodes and 100% in lymph nodes in the deep inguinal chain and in the region of the obturator. According to the authors, small lymph nodes, measuring between 0.7 and 1.1 cm, can be detected as metastatic, due to the intense and usual pattern of FDG uptake in this type of malignancy. There was a significant positive result between the degree of uptake and the maximum diameter of the lymph nodes considering lymph

nodes up to 2.5 cm in diameter. However, malignant lymph nodes may not present suspicious uptake and the detection of micrometastases (<2 mm) is an intrinsic limitation of the method (26,38,39).

Graafland *et al.* (40) staged 18 patients with SCCP using ¹⁸F-FDG PET-CT who had cytologically confirmed unilateral or bilateral inguinal metastases. The method showed a sensitivity of 91% and a specificity of 100%. The diagnostic accuracy was 96%, the positive predictive value was 100% and the negative predictive value was 94% in detecting metastatic pelvic lymph nodes.

In a prospective study that evaluated patients with SCCP and impalpable lymph nodes, PET-CT was unsatisfactory in detecting lymph node tumor involvement (41).

Scher *et al.* (38) suggest the possibility of applying DSNB together with PET-CT to try to reduce the risk of undiagnosed micrometastases. These combined methods can achieve a sufficiently high degree of diagnostic efficiency to avoid lymphadenectomy, which is usually associated with increased morbidity.

The variety of imaging methods, the unique availability of each of them, the experience of radiologists and nuclear physicians, and the paucity of prospective studies on this uncommon disease impose different diagnostic choices, often on an individual basis. The improvement of techniques, greater availability of equipment and the appropriate combination of exams for each case should be the way to minimize current failures.

According to the NCCN guidelines on penile cancer (42), both standard and modified ILND, as well as dynamic sentinel lymph node biopsy, should be indicated in patients with penile cancer in the absence of palpable inguinal lymph nodes, when there is a high risk for nodal metastasis in the primary penile tumor (lymphovascular invasion, surgical staging greater than or equal to pT1G3 or tumor with stage equal or greater than T2 and any grade, as well as the presence of more than 50% of poorly differentiated tumor). DSNB is only recommended if the attending physician has experience with this type of approach. If metastatic lymph nodes are found on DSNB, ILND should be performed. If ILND detects 2 or more ipsilaterally positive inguinal lymph nodes, a pelvic lymphadenectomy (PLND) should also be performed at the same time of ILND or also be performed in case an extranodal extension is found in the final pathological review. A bilateral PLND should be considered at the time or after a bilateral ILND in patients with 4 or more metastatic inguinal lymph nodes

considering both sides operated.

Lymphadenectomy

Between 1972 and 1987, Ornellas *et al.* (43) analyzed 200 consecutive open radical lymphadenectomies comparing different types of incisions. When the Gibson incision was used, complication rates dropped drastically with a necrosis rate in the order of 5%. In another study in which we analyzed 688 operated patients, we concluded that the stage and histological grade of the tumor influenced the prognosis of the disease. Metastatic involvement and its extension to the inguinal region proved to be the most important prognostic factors when considering survival in our patients. Immediate lymphadenectomy is therefore indicated for all patients with significant risk of lymph node metastases. Frequent and long-lasting follow-up is essential for all patients, as we observe recurrences at 8, 10 and 25 years after the primary treatment (14).

Updating these data, Koifman *et al.* (44), studied the results obtained with open radical ILND, performed bilaterally in 170 patients. There were 35 complications (10.3%), of which 25 (71.4%) were minor and 10 (28.6%) were major. Lymphedema was observed in 14 patients (4.1%), seroma in 4 (1.2%), scrotal edema in 3 (0.9%), skin edge necrosis in 3 (0.9%), lymphocele in 3 (0.9%), surgical wound infection in 2 (0.6%), flap necrosis in 2 (0.6%), surgical wound abscess in 2 (0.6%) and deep venous thrombosis in 2 (0.6%). Complication rates among patients treated with prophylactic or therapeutic lymphadenectomy did not show significant differences. Our contemporary series showed a lower incidence of complications, such as wound infection, skin flap necrosis, lymphocele and lymphedema. So far, this series has the lowest incidence rate of complications in the international literature.

More recent surgical procedures, such as laparoscopic ILND and robot-assisted ILND, have been used to try to reduce ILND morbidities without compromising oncological treatment. Although limited, available data indicate that these minimally invasive techniques are safe and have fewer perioperative morbidities. Different treatment approaches, including open, laparoscopic and robotic surgery, appear to have similar results and efficacy when considering the yield in obtaining lymph nodes (45).

Gkegkes *et al.* (46) studied the results of robotic ILND in 51 patients with penile cancer. No intraoperative complications were found. One case of conversion to open surgery has been reported. According to this review, so

far the role of robotics in ILND is unclear, although this type of approach appears to be safe and effective from an oncological point of view and morbidity rates are relatively lower when compared to open surgery.

Palliative surgery is indicated for patients with advanced penile cancer who have large metastatic areas in the groin. These patients have fixed or ulcerated lymph nodes, unilaterally or bilaterally, which need to be resected together with the skin attached to them. This approach usually results in large local defects that are difficult to correct surgically. In the past, they were considered beyond any therapeutic surgical possibility. When the defects caused by the excision of the lesion are large enough to preclude primary closure of the surgical wound, several reconstructive techniques can be used. As SCCP is an infrequent neoplasm, there are no prospective studies on the reconstruction of inguinal defects in this disease. Thus, new treatment strategies have to be developed. Tensor fascia lata myocutaneous flaps, abdominal myocutaneous flaps or even free skin grafts can be used to reconstruct the open areas resulting from the resection of the metastatic tumor mass. Recently, the results of primary inguinal surgical debulking (PRISD) for locally advanced penile cancer were published. The reconstruction of the affected area was performed with myocutaneous flaps (47). In this study, with 42 patients, bilateral PRISD was performed in 10 patients (23.8%) and unilateral PRISD with contralateral radical inguinal lymphadenectomy (RIL) in 32 (76.2%) reaching a total of 84 lymphadenectomies. Sixty-two reconstructions were performed with a myocutaneous pediculate flap reconstruction (MPFR), 52 with a tensor of fascia lata (TFL) flap and 10 with a gracilis flap (GF). Regarding complications, there were 53, 49 related to PRISD with MPFR and 4 to RIL. Adjuvant chemotherapy was used in 16 patients. The mean follow-up was 10.8 months. Median overall survival was 14.0 months for patients undergoing PRISD plus adjuvant chemotherapy versus 6.0 months when surgery was used alone ($P=0.006$). While PRISD alone is unlikely to improve long-term survival, it may lead to temporary local disease control. Although this procedure is feasible, it is associated with a high incidence of complications and needs to be performed by experienced multidisciplinary teams.

Recurrence

According to the NCCN guidelines on penile cancer (42), when an invasive tumor recurs after initial organ-sparing

treatment, it should be treated according to the stage of recurrence. Patients with recurrence in the inguinal region have a poor prognosis, with a median survival of less than 6 months. The ideal approach remains elusive. If no ILND or radiotherapy (RT) has been performed previously, primary treatment with an inguinal surgical approach can be followed. If the patient has already undergone lymphadenectomy or RT, subsequent line therapies include chemotherapy followed by lymphadenectomy, a surgical approach alone, or chemoradiotherapy if the patient has not previously undergone RT. One study suggests that a new ILND may be beneficial for patients with penile cancer with locally recurrent metastases. Although these procedures can potentially be curative, patients should be warned of the high incidence of postoperative complications (48).

Chakiryani *et al.* (49) confirmed that 31.9% of the patients had recurrence after ILND associated with a higher surgical staging of the lymph nodes and more than 95% of the distant, inguinal and pelvic recurrences occurred in approximately 48 months. These findings suggest that surveillance, beyond this time interval, has low yield. However, local recurrences occurred after this long period of time, emphasizing the need for long-term primary surveillance.

Salvage inguinal surgery may be a potentially curative treatment in patients with locally recurrent inguinal lymph node metastases if the metastatic lymph node mass is completely resected and in the absence of undetected micrometastases. However, the high probability of postoperative complications in this type of salvage surgery should be made known to patients (48).

Chemotherapy

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy followed by treatments that preserve the penile shaft should be considered investigational despite promising results.

According to the NCCN guidelines on penile cancer (42), the preferred neoadjuvant chemotherapeutic regimen would be the combination of paclitaxel, ifosfamide and cisplatin (TIP). This chemotherapeutic treatment is used before ILND in patients with penile cancer with fixed or mobile inguinal lymph nodes of 4 cm or more that prove to be positive for the disease (50).

A bulky resectable disease should be treated in a multidisciplinary way, as it will rarely be cured with a single treatment modality. Primary unresectable tumors

(T4) can be reduced after chemotherapy. As mentioned in the previous paragraph, patients with positive lymph nodes greater than or equal to 4 cm may benefit from neoadjuvant chemotherapy. Stable patients or those with partial and complete remission may benefit from surgical treatment after systemic chemotherapy (51,52). Neoadjuvant chemotherapy with paclitaxel, ifosfamide and cisplatin was used by Pagliaro *et al.* (53) in 30 patients with stage N2 or N3 without distant metastases. Responsiveness to chemotherapy, absence of bilateral residual tumor, and absence of extranodal extension or skin involvement were associated with longer time to progression and increased overall survival. A patient staged as Tx, N2–3, M0 should receive 4 cycles of TIP. If the disease remains stable or decreases after chemotherapy, surgical treatment may be indicated with curative intent.

Likewise, combination of 5-fluorouracil (5-FU) with cisplatin was able to generate, in some series, objective responses in up to 66% of patients, allowing salvage surgery by transforming irreparable inguinal metastatic lesions into resectable ones (48,54-56).

Adjuvant chemotherapy

When there is a high risk of local recurrence and/or systemic dissemination, as well as patients with a poor prognosis, characterized by: bilateral lymph node involvement, extracapsular lymph node dissemination, more than two lymph nodes affected by the disease, presence of compromised lymph nodes greater than 2 cm in diameter or involvement of pelvic lymph nodes may be beneficial adjuvant chemotherapy.

If chemotherapy was not administered preoperatively and the tumor has the high-risk characteristics referred in the previous paragraph, it is fair to extrapolate using data obtained with neoadjuvant chemotherapy and it is reasonable to administer 4 cycles of TPI in the adjuvant setting. The use of 5-FU plus cisplatin can also be considered as an alternative to TIP in the adjuvant setting. However, according to the NCCN guidelines (42), there are not enough data to form conclusions about the use of adjuvant chemotherapy.

Adjuvant chemotherapy was also evaluated in patients with positive pelvic lymph nodes resected by PLND. Less than half of these patients received adjuvant chemotherapy treatment. Compared with patients who did not receive chemotherapy, these patients had a higher median overall survival. In this retrospective multi-institutional study, adjuvant chemotherapy was shown to be an independent

factor in improving overall survival based on multivariate analysis (57).

Adjuvant concurrent RT and chemotherapy

Although chemoradiation is used in the initial treatment of patients with locally advanced squamous cell carcinoma of the head and neck, anal canal and vulva, evidence to support its application in penile cancer is lacking. The lack of studies regarding penile cancer was the basis for the international cooperation to develop InPACT (58): the International Penile Advanced Cancer Trial in 2017 in order to prospectively determine the potential benefits of chemotherapy or chemoradiation following lymph node dissection in patients with clinical evidence of inguinal lymph node metastases. InPACT is accruing well and will provide level 1 evidence on how to best combine surgery, RT, and chemotherapy in management of node positive penile cancer.

However, several current studies suggest that adjuvant RT has a role to play in the treatment of men with pN3 penile squamous cell carcinoma (59-61).

In another study carried out with patients with nodal positivity limited to the inguinal region, adjuvant RT was shown to be superior to chemotherapy (62).

Another study compared patients who received adjuvant RT plus chemotherapy with patients who received only adjuvant chemotherapy. In conclusion, adjuvant RT + adjuvant chemotherapy was associated with improved cancer-specific survival in patients with penile cancer who had extracapsular nodal extension after inguinal surgery (63).

Regarding pelvic lymph nodes, inguinopelvic RT may benefit for regional control in patients with positive pelvic lymph nodes, but this appears to be limited to those without extranodal extension (64).

Furthermore, another study showed an advantage in using adjuvant pelvic RT to treat patients with penile cancer and positive pelvic lymph nodes. The use of RT improved survival and decreased recurrence in this population (65).

However, according to Yuan *et al.* (66), similarly to primary penile lesions, most nodal metastases are genomically radioresistant with significant heterogeneity. According to these authors, optimal therapeutic gain can be achieved by stratifying the combination of clinical-pathological parameters, genomic heterogeneity, and radiation dose prescription based on its genome-based radiosensitivity index.

Chemotherapy for systemic disease

Patients with disseminated disease have a poor prognosis,

and chemotherapy is used as palliation. In these cases, treatment usually produces partial and transient responses. The emergence of new chemotherapeutic agents including molecularly targeted drugs may in the future change the perspective in the treatment of this rare disease. However, common efforts are needed in the creation of international protocols in order to define the best applicability of chemotherapy in the future.

Patients whose metastatic carcinoma of the penis progresses or recurs after cisplatin-based first-line chemotherapy have poor responses to the salvage treatments described. The median overall survival time of these patients is less than 6 months. Emphasis should be placed on clinical trials to develop effective therapy in this setting (67).

The subsequent line of chemotherapy for metastatic or recurrent disease (42) includes pembrolizumab if the tumor is unresectable or metastatic, if microsatellite instability is high (MSI-H) or mismatch repair is deficient (dMMR). Pembrolizumab can also be used if the tumor has progressed after previous treatment and there are no satisfactory alternative treatment options (68).

There is no pattern of subsequent systemic therapy. Palliative use of second-line therapy is limited by lack of evidence of its usefulness (67). Useful in Certain Circumstances, Paclitaxel or cetuximab can be used in patients who have not previously been treated with an agent from the same class of agents aforementioned (69,70).

Limitations

Regarding the development of specific chemotherapy drugs for the disease, penile cancer is a neglected neoplasm. It is rare and occurs mainly in patients of low social status whose hygiene is precarious. Due to the small number of patients usually presented in each published series, it is difficult to assess the effectiveness of the proposed treatment. In this review, I have tried to include the most relevant studies on the subject and also consult the NCCN and EAU guidelines. Larger series are obtained over many years of patient observation. Randomization of patients who should be treated with chemotherapy remains a challenge. The number of these patients is very small and the analysis of cases is hampered by the large observation time interval. Another limitation of long-term studies is changes in treatment and chemotherapy regimens that vary over the years. The correct thing would be to produce prospective studies with the collaboration of multiple institutions specialized in the treatment of penile cancer.

Conclusions

The most important prognostic factor for reduced survival in penile cancer is the involvement of the inguinal region by metastases. Inguinal recurrence of the disease indicates a poor prognosis. Chemotherapy can shrink previously unresectable primary tumors (T4), allowing for a more conservative surgical approach. Neoadjuvant chemotherapy allows salvage surgery by transforming irreparable inguinal metastatic lesions into resectable ones. The indicated neoadjuvant chemotherapeutic treatment would be the TIP. This chemotherapeutic treatment is used before ILND in patients with penile cancer with fixed or mobile inguinal lymph nodes of 4 cm or more that are positive for the disease. Combination of 5-FU with Cisplatin was able to generate, in some series, objective responses, allowing salvage surgery. There are not enough data to form conclusions about the use of adjuvant chemotherapy. When there is a high risk of local recurrence and/or systemic spread, patients may benefit from adjuvant chemotherapy and/or RT. Several current studies suggest that adjuvant RT has a role to play in the treatment of men with pN3 penile squamous cell carcinoma. Adjuvant RT + adjuvant chemotherapy appears to be associated with improved cancer-specific survival in patients with penile cancer who have extracapsular nodal extension. RT may also benefit for regional control in patients with positive pelvic lymph nodes. Chemotherapy should be used as palliation in patients with disseminated disease and poor prognosis. Paclitaxel or cetuximab can be used in patients who have not previously been treated with an agent of the same class.

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Footnote

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