Perioperative treatment of high-risk penile squamous cell carcinoma (SCC)

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Background: definition of "high-risk" penile cancer

The presence and extent of metastases dictate survival in penile SCC. Penile SCC has a particular tendency toward lymphatic spread to the superficial and deep inguinal lymph nodes and, subsequently, to the pelvic nodes, prior to further distant dissemination. A literature review showed that after ilio-inguinal lymph node dissection (ILND) the five-year survival for men with negative inguinal nodes is 93% to 100%, for those with one positive node or unilaterally positive nodes it is around 80%, for >2 unilaterally positive nodes it is about 50%, and for bilaterally positive nodes, extranodal extension (ENE) or positive pelvic nodes it is approximately 10% [1]. Patients with advanced penile SCC usually die because of complications due to uncontrollable loco-regional growth or from distant metastases, with mean survival then approaching 7–10 months [2]. It has been suggested that adjuvant therapy is advisable when there are two or more positive nodes, extranodal extension of cancer or pelvic node metastasis [3,4]. More recently, it has been suggested that new imaging techniques like MRI and positron emission tomography and fine-needle aspiration cytology could help define prognostic categories and allow neoadjuvant strategies [5]. Considering survival curves of large series high-risk penile cancer can be defined as stage III or localised stage IV, referring to T4, N2 or N3 or primary tumour invading adjacent structures, metastases in multiple or bilateral inguinal lymph nodes, ENE, fixed inguinal nodes or pelvic nodes [6]. Successful management of high-risk patients with penile SCC involves combination therapies of surgery, chemotherapy (CT), and/or radiation therapy (RT).

Chemotherapy

There are several published phase II clinical trials of combination chemotherapy, mostly evaluated as palliative treatments in patients with distant metastases or fixed inoperable inguinal nodes, but also, more recently, in a neo-adjuvant setting. Being a rare disease, these trials are small and no study has ever been replicated as a confirmatory measure. There are also no randomised trials, and comparison of treatment results from different trials is complicated by differences in patient characteristics such as prior therapy and stage of disease. Table 1 summarises the data from five different combination regimens reported since 1990 and, for comparison, two earlier studies of single-agent chemotherapy. A regimen would be of interest if it achieved an ORR significantly greater than 30% without producing life-threatening toxicity. Following early reports providing evidence of some efficacy of bleomycin (B), methotrexate (M), and cisplatin (P) as single drugs [8], A SWOG phase II study of BMP included 40 evaluable patients. The response rate was 32.5% (5 CR, 8 PR), being within the 95% CI range for single-agent cisplatin [9]. There were five treatment-related deaths, one from infection and four from pulmonary complications [10]. The fluorouracil/cisplatin study [11] was retrospective and very small, with only eight patients, making it difficult to reach any firm conclusions regarding efficacy. The irinotecan/cisplatin study [7] conducted by the EORTC was prospective, and larger, with 26 evaluable patients, but was interpreted as a negative result by the authors because the response rate had an 80% confidence interval (18.8–45.1%), extending well below 30%. However, seven initially inoperable patients underwent ILND, three with negative histopathology. The combination of paclitaxel, ifosfamide, and cisplatin (TIP) phase II study was designed as neoadjuvant for patients with N2 or N3 patients without distant metastases [13]. Thirty men received chemotherapy, of whom 15 (50.0%) had an objective response and 22 (73.3%) subsequently underwent surgery. Three patients had no remaining tumour on histopathology. Nine patients (30.0%) remained alive and free of recurrence (median follow-up, 34 months;

Table 1
Series of chemotherapy for advanced penile cancer[a]

Author (year)	Number of patients (evaluable)	Drug or regimen	Prospective study
Ahmed et al. (1984) [8]	13 (13)	Methotrexate	No
	14 (12)	Cisplatin	No
	14 (14)	Bleomycin	No
Gagliano et al. (1989) [9]	26 (26)	Cisplatin	Yes
Shammas et al. (1992) [10]	8 (8)	Fluorouracil Cisplatin	No
Haas et al. (1999) [11]	45 (40)	BMP	Yes
Skeel et al. (2003) [12]	18 (16)	Interferon α 13-CRA	Yes
Theodore et al. (2008) [7]	28 (26)	Irinotecan Cisplatin	Yes
Pagliaro et al. (2010) [13]	30 (30)	TIP	Yes

[a] Adapted from Pettaway [14].
BMP, bleomycin, methotrexate, cisplatin; 13-CRA: 13-cis-retinoic acid; TIP, paclitaxel, ifosfamide, cisplatin.

range, 14–59 months). A retrospective neoadjuvant series with five different chemotherapy regimens in 19 patients with penile SCC and unresectable nodes reported similar results with eight long-term survivors out of nine responding patients [14]. The preliminary report of a neoadjuvant series with taxanes in combination with cisplatin and fluorouracil showed a benefit in three of the six patients [15]. Selected patients with advanced, unresectable primary tumours or bulky regional lymph node metastases appeared to benefit from neoadjuvant strategy with post-chemotherapy lymphadenectomy. The role of adjuvant chemotherapy can only be extrapolated from data in the neoadjuvant setting.

Radiotherapy

There are no high-level evidence publications in the literature supporting individual approaches with RT, but there are several small series providing informative data, and experience with chemo-radiation therapy of squamous cell cancers from other sites (vulvar and anal canal) that support combination therapy for unresectable penile cancer. One of the largest series demonstrating a benefit of RT for lymph node metastases from penile cancer was published by Ravi [16]. In this series of 120 patients, 33 patients were treated with preoperative RT at 40 Gray (Gy) over four weeks and subsequently had inguinal lymphadenectomy. Of note, after RT and surgery only 8% had evidence of extranodal extension (ENE) and 3% recurred within the groin. This is relevant as in a prior report within a contemporary time frame the incidence of ENE was 33% among patients treated with surgery alone and groin recurrence was noted in 19%. The difference for both ENE and local recurrence was statistically lower ($P \leqslant 0.01$ and 0.03 respectively). The data are strongly suggestive, but not definitive, evidence that preoperative RT for nodes $\geqslant$4 cm without skin fixation improved local control. However preoperative radiation to the groin significantly increased the healing complications. Palliative RT ameliorated symptoms in 56% of patients with fixed groin nodes. However, pelvic and/or para-aortic RT was ineffective in patients with pelvic node metastases (Table 2).

Main recommendations of the Societé Internationale d'Urologie (2009) concerning perioperative treatment of advanced penile cancer [17]

(1) Treatment with a cisplatin-containing regimen in stage IV penile cancer should be considered, as responses do occur and this may facilitate curative resection. The use of the best combination remains to be determined, but use of bleomycin in these patients was associated with an unacceptable level of toxicity.
(2) Surgical consolidation to achieve disease-free status or palliation should be considered in fit patients with a proven objective response to systemic chemotherapy.
(3) Preoperative inguinal radiotherapy among patients with nodes $\geqslant$4 cm without skin fixation may improve surgical resectability and decrease local recurrence. The morbidity of this combined strategy requires further study.

Conflict of interest statement

The author has no conflict of interest to disclose.

Table 2
Perioperative radiation therapy for lymph node

Time of treatment	Indication	No. of groins	No. of patients	CR	PR	<PR	Palliation of symptoms	Subsequent groin dissections	5-Year DFS (%)
Preoperative: Inguinal RT	Nodes >4cm in size not fixed to underlying structures or overlying skin	38	33	1	6	31		38	23 (70)
	Nodes of any size fixed to overlying skin but mobile	14	12		2	12		7	2 (17)
Postoperative: Inguinal RT	Perinodal infiltration in the inguinal region	14	12						1 (8)
Pelvic RT	Metastatic pelvic nodes on lymphadenectomy	20	18						0
Pelvic RT Pelvic and para-aortic RT	Metastatic pelvic nodes on lymphadenectomy	4	4						0
Palliative inguinal RT	Nodes fixed to underlying structures with or without skin infiltration	66	41	1	2	63	23	2	1 (2)

[a] Adapted from Ravi et al. [16]

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