ORIGINAL ARTICLE – CANCER RESEARCH

Adherence to the EAU guidelines on Penile Cancer Treatment: European, multicentre, retrospective study

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Abstract

Purpose The European Association of Urology (EAU) guidelines for penile cancer (PC) are exclusively based on retrospective studies and have low grades of recommendation. The aim of this study was to assess the adherence to guidelines by investigating the management strategies for primary tumours and inguinal lymph nodes.

Methods We retrospectively reviewed the clinical charts of 176 PC patients who underwent surgery in eight European centres from 2010 to 2016. The stage and grade were assessed according to the 2009 AJCC–UICC TNM classification system. To assess adherence rates, we compared theoretical and practical adherence to the EAU guidelines.

Results Overall, 176 patients were enrolled. Partial amputation was the most frequent surgical approach (39%). 53.7% of tumours were stage Tis-T1b and the remaining 46.3% were stage T2-T4. Palpable lymph nodes were detected in 30.1% of patients and 45.1% underwent lymphadenectomy (LY). A sizeable group of tumours (43.2%) were N0. For primary treatment, adherence to the EAU guidelines was good (66%). In non-adherent cases, reasons for discrepancy were patient's choice (17%), surgeon's preference (36%), and other causes (47%). For LY, the guideline adherence was 70%, with either patient's or surgeon's choice or other causes accounting for discrepancy in 28, 20, and 52% of non-adherent cases, respectively.

Conclusion Adherence to the EAU guidelines for PC was quite high across the eight European centres involved in the study. This notwithstanding, strategies for further improvement should be developed and evenly adopted.

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Introduction

Penile cancer (PC) is a rare malignancy and a potentially mutilating disease for men. In the United States and Western countries, it accounts for 0.4–0.6% of all malignancies (Clark et al. 2013). The major risk factor for PC is an uncircumcised penis (Maden et al. 1993). Other factors include HPV infection, smoke, and low socio-economic status (Rubin et al. 2001; Harish and Ravi 1995; Daling et al. 2005). About 95% of penile cancers are squamous cell carcinomas (SCC) and can develop anywhere on the penis (Christodoulidou et al. 2015). Most commonly, these tumours appear as a lump or nodule (47%), an ulcer (35%), an erythematous lesion (17%), or an incidental finding at circumcision (0.7%) (Hernandez et al. 2008). If treated at an early stage, PC has a cure rate of 80%. Pathologic stage or grade of the primary tumour and subsequent locoregional lymph node metastasis drive survival, with node-positive patients having 5-year survival

rates ranging from 20 to 80% (Pandey et al. 2006). The optimal treatment for primary tumour depends on lesion's size, location, and possibility of oncological radicality preserving both quality of life and sexual satisfaction. Since PC is a rare disease, the treatment is not always uniform and often depends on surgeon's experience and patient's preferences. For example, radical inguinal lymph node dissection (ILND) is the standard of care for node-positive patients and is potentially curative in half of the cases (McDougal 2005); however, its complexity and associated high degree of morbidity (wound healing and lymphoedema) often discourage use (Thuret et al. 2011). Theoretically, guidelines should provide evidence-based guidance to physicians and patients alike. Although following established guidelines has been found to improve patient outcomes and enhance consistency of practices, some studies on solid cancer treatment report extremely variable adherence rates, ranging from 40 to 99% (Heins et al. 2016). The aim of this study was to evaluate adherence to the EAU guidelines in a multicentre series of patients surgically treated for penile cancer.

Materials and methods

We retrospectively reviewed the clinical charts of 176 PC patients who underwent surgery in 8 European centres from 2010 to 2016. The study was approved by the Ethics Committee of each participating institution and all the procedures were performed in accordance with the Declaration of Helsinki. Information on demographics, patients' comorbidities, circumcision, site of primary lesion, local therapy, lymph node management, and histopathological data was collected and analysed. Staging was as per the 2009 AJCC–UICC TNM classification system and was performed with a combination of physical examination and CT and/or MRI. Treatment of the primary tumour and the decision to proceed to inguinal lymph node dissection were established according to local protocols based on the 2009 EAU guidelines. For patients with penile carcinoma in situ (CIS), the European Association of Urology recommends topical chemotherapy with 5% fluorouracil and imiquimod (Alnajjar et al. 2012). For Ta/T1 lesions, laser ablation is a valid treatment (Colecchia et al. 2009). For penile glans tumours, glans resurfacing and glansectomy are preferred (Pizzocaro et al. 2010). When tumours extend into the corporeal bodies, urethra, and adjacent structures (T2–T4), partial penectomy provides excellent oncologic control (Opjordsmoen and Fossa 1994). When a negative margin cannot be achieved, or a large fungating tumour is present, total amputation with perineal urethrostomy is recommended (Garaffa et al. 2009). As regards inguinal lymph node management, patients with clinically node-negative (cN0) pTis, pTa, and pT1a tumours are at low risk of inguinal metastasis and are suitable candidates for observation. For patients with intermediate-to high-risk tumours (pT1b, T2–T4), either modified inguinal lymph node dissection (ILND) or dynamic sentinel node biopsy (DSLNB) is recommended (Hughes et al. 2010). Patients with clinically positive lymph nodes (cN1/cN2) are at high risk of metastatic disease and radical ILND is in order. Enlarged fixed inguinal lymph nodes (cN3) require multimodal treatment by chemotherapy followed by radical ILND in clinically responsive cases (Pizzocaro et al. 2010). In our study, indications for pelvic lymph node dissection were > 2 proven inguinal metastases, involvement of the femoral (Cloquet's) node, and radiological suspicion of pelvic lymph node involvement. Follow-up was by a combination of physical examination and imaging based on risk stratification and was updated by recall to the clinic. Theoretical adherence to the EAU guidelines for primary surgery and lymphadenectomy was assessed for each case. A case was considered adherent when the surgical approach was perfectly aligned with the guidelines. For non-adherent cases, reasons for discrepancy were analysed and grouped as follows: (1) patient's choice; (2) surgeon's preference; and (3) other. Statistical analysis was performed using SPSS (version 25.0). Data evaluation confirmed a non-normal distribution of the study dataset. Intergroup differences in medians for quantitative variables were tested using the Kruskal–Wallis one-way analysis of variance, and differences in distributions for categorical variables were calculated with a Chi square test. Using multiple logistic regression with the ENTER method, the statistically significant age-adjusted variables as assessed by univariate analysis were entered and investigated as predictors of adherence to the EAU guidelines. The threshold for significance was set at alpha = 0.05. Data are presented as mean ± standard deviation (SD). Odds ratios and 95% confidence interval (CI) were calculated for the parameters in each group using "non-adherence" as the reference group.

Results

Patients' demographics, surgical details, and histopathological findings are reported in Table 1. Overall, 176 patients were enrolled (mean age 66 ± 11.3). All patients had histopathologically confirmed squamous cell carcinoma of the penis. Tumours were mainly located at the glans (55%), 38% were stage pT1, and 83% had negative surgical margins. Penile partial amputation was the most common surgical approach (39%). At diagnosis, 30.1% of patients had palpable inguinal lymph nodes. ILND was performed in 45.1% of patients (15% cN0 and 80% cN1/cN2; the remaining 5%, although meeting the EAU criteria, declined surgery). Nodal status was available for 74 patients: 32 patients were pN0, 19 were pN1, and 23 were pN2. For primary treatment, adherence to the EAU guidelines was good (66%) (Fig. 1). In
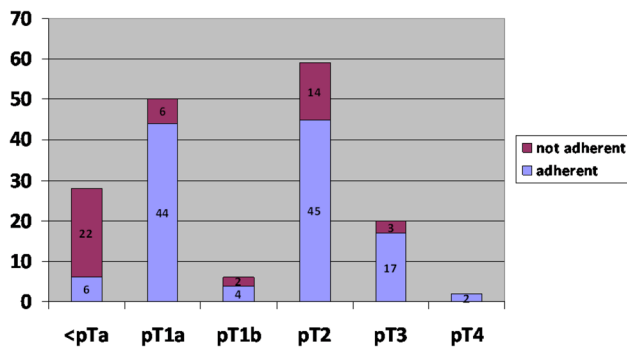
Fig. 1 Adherence distribution based on pT stages

non-adherent cases, reasons for discrepancy were patient's choice (17%), surgeon's preference (36%), and other causes (47%) (Table 2). For lymph node treatment, guideline adherence was 70% (Fig. 2), with either patient's or surgeon's choice or other causes accounting for discrepancy in 28, 20, and 25% of non-adherent cases, respectively (Table 2). Univariate analysis showed no significant differences between adherent and non-adherent patients, whereas at multivariate analysis, the stage appeared to be the only predictor of adherence for primary treatment (OR 2.61, 95% CI 1.34–5.06, $p = 0.005$) (Table 3). At a mean follow-up of 2 years, 126 patients were alive, 35 had died from cancer progression, and the remaining 15 had died of other causes.

Discussion

Clinical guidelines provide scientifically informed guidance to both physicians and patients for making appropriate health care decisions. They have the potential to improve outcomes, enhance consistency of practices across institutions, and support quality improvement activities (Heins et al. 2016; Catalona 1988). The European Association of Urology constantly produces and updates guidelines covering all fields of urology. The EAU guidelines on PC were first published in 2001 and received a major update in 2009, concurrently with the release of a new version of the TNM Classification of Malignant Tumors (TNM). Although most urologists are familiar with the EAU recommendations, adherence may be poor for several reasons. First of all, penile cancer is a rare disease in industrialised countries, which means that the approved guidelines are mostly based on small, methodologically weak studies (e.g., retrospective studies, opinion letters, case reports etc.). As a consequence, they will have a low level of evidence and degree of recommendation. Numerous factors may influence adherence in clinical practice. Although treatment of the primary tumour can be curative for PC, guideline recommendations are not always followed, especially when a generally poor prognosis and a

Table 1 Patients' demographics: clinical, surgical and pathological characteristics ($N = 176$)

	N	%
Age, mean (SD)	66.5 (11.3)	–
Comorbidities		
Diabetes	40	22.7
Hypertension	70	39.7
Cardiovascular disease	16	9
Dyslipidaemia	8	4.5
Multiple comorbidities	22	12.5
No comorbidities	20	11.6
Circumcision (14 missing)		
Yes	70	43.5
No	92	56.5
Site of lesion		
Prepuce	20	10.8
Glans	96	54.9
Both	60	34.3
Size of lesion [mean (SD)]	3 (1.8)	
Palpable lymph nodes		
No	123	69.9
Yes	53	30.1
Histologic findings		
pTNM		
Tis–T1a	94	53.7
T1b–T4	81	46.3
Grading		
G1	65	37.1
G2	83	46.9
G3	28	16
Vascular invasion		
No	138	78.9
Yes	38	21.1
Lymphovascular invasion		
No	140	79.4
Yes	36	20.6
Surgical margins		
R0	147	83.4
R1	29	16.6
Nodal status		
pN0	32	43.2
pN1	19	25.7
pN2	23	31.1
Type of surgery		
Circumcision	12	6,9
Local excision	42	24
Glansectomy	27	15.3
Partial penectomy	69	38.9
Total penectomy	26	14.9
Lymphadenectomy		
No	96	54.9
Yes	80	45.1

Table 2 Adherence rates for primary treatment and lymphadenectomy and reasons for non-adherence

	Adherence (primary treatment)		Adherence (lymphadenectomy)	
	N	%	N	%
Yes	116	65.7	122	69.7
No	60	34.3	54	30.3
Surgeon's choice	22	35.6	11	20
Patient's choice	10	17	16	28
Other causes	28	47.5	27	52
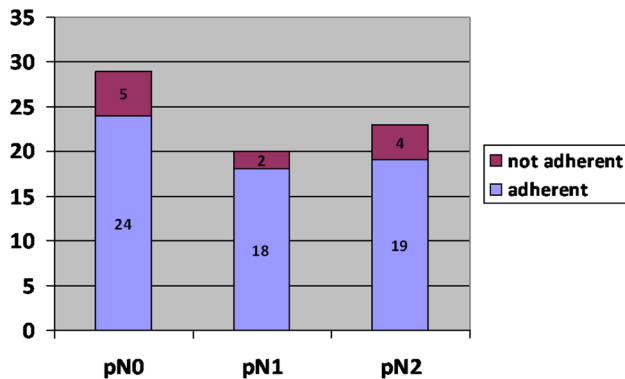
Fig. 2 Adherence distribution based on pN stages

high rate of serious side effects are expected (Leone et al. 2017; Pizzocaro and L Piva 1988; Breen et al. 2015). For example, physicians may be less likely to adhere to established treatment recommendations when patients have severe comorbidities or poor general health. In our study, treatment of the primary tumour was in line with the guidelines in 66% of cases, with stage being the only significant predictor of adherence (OR 2.61, 95% CI 1.34–5.06, $p = 0.005$). Not surprisingly, physicians are more likely to follow procedures with which they are more familiar. Nowadays, PC is not

a topic of frequent discussion in clinical practice (Cabana et al. 1999). It is also an emotive disease and both under- and overtreatment can have considerable short- and long-term repercussions (Kumar et al. 2012). The patient is actively involved in the clinical decision-making process, perhaps even more so than for any other kind of tumour given the potentially devastating effects on quality of life and mental well-being. Our data confirm that the wider discrepancy between guidelines and clinical practice is typical of localised tumours that in theory should be better treated with organ-preserving techniques. It is worth noting that there currently is no widespread definition of penile sparing surgery. Historically, treatment was by radical or partial amputation with a 2-cm margin for oncologic efficacy. Over time, guidelines began to favour a more conservative approach whenever possible. Local recurrence has a minimal impact on long-term survival. Horenblas et al.'s multivariate analysis demonstrated no difference in cancer-specific survival for patients treated with penile sparing surgery vs. partial amputation (Djajadiningrat et al. 2004). Despite current trends, some less experienced centres continue to have an all-too radical approach which is not in line with the latest guidelines. A more extensive experience in treating PC would doubtlessly allow for the safer use of conservative techniques.

Our study was not geared to describe reasons for non-adherence in detail, but individual choice appears to be an important factor for both patients (24%) and physicians (34%), the latter often mentioning lack of training and skill as the reason for departing from recommendations. In the remaining 42% of cases, we were unable to establish the exact reasons for non-compliance. The EAU guidelines recommend ILND in cN0 patients with pT1b and T2–T4 tumours, as well as in all cN1/cN2 patients. Despite lymph node status being the primary determinant of survival in penile carcinoma (D'Ancona et al. 2004), only a fraction of patients who are candidates for ILND undergo the procedure. Our results indicate an overall ILND rate of 45.1%,

Table 3 Population's characteristics based on the 2016 EAU guidelines; adherence rates for primary treatment

	Non-adherent patients (60/176) 35%	Adherent patients (115/176) 65%	p
Age (years) [mean (SD)]	68.3 (11.2)	65.5 (11.2)	0.113
Size (cm) [mean (SD)]	3 (2.3)	3 (1.65)	0.387
Circumcision (%) (missing = 16)	21/53 (13.1%)	48/107 (30%)	0.324
PT stage (%)			
Tis–T1a	41/60 (23.4%)	53/115 (30.3%)	0.004
T1a–T4	19/60 (10.9%)	62/115 (35.4%)	
PN stage (%)			
N0	8/17 (10.8%)	24/57 (32.4%)	0.741
N1	5/17 (6.8%)	14/57 (18.9%)	
N2	4/17 (5.4%)	19/57 (25.7%)	

a figure consistent with previous estimates (ILND ranges 39.1–43.6%, for all SCC stages) (Ficarra et al. 2005; Ornellas et al. 2008). Adherence to the EAU ILND guidelines was 70% in our study. This is surprisingly high, even admitting that clinical practice should strive for maximum correspondence with international recommendations. The result is also in sharp contrast with the findings by Leijte et al., whose analysis of compliance with the NCI ILND guidelines reported adherence rates of only 27.6% (Leijte et al. 2008). Non-adherence may be ascribed to lack of surgical experience or insufficient familiarity with inguinal lymphadenectomy. Practical constraints may also have a part, for example, in the non-ubiquitous availability of sentinel node biopsies.

Our study is not devoid of limitations. First, its retrospective design limits the quality of the data. Second, a central pathology review could have contributed to higher accuracy of pathologically assessed variables, and hence the lack of it may represent another weakness. However, none of the previously reported multi-institutional studies relied on central pathology (Leijte et al. 2008). Third, complications and length of hospitalisation could not be analysed because the database was not designed to take these parameters into account. Fourth, the small number of patients limited deep survival analysis, which is important for future research. Finally, our study cohort originates from eight European centres, each with its own definition of disease progression and varying levels of surgical skills. Despite this obvious limitation, all multicentre studies benefit from greater generalisability of results, which increases proportionally to the number of surgeons and clinical sites involved.

Conclusion

Adherence to the EAU guidelines for PC was quite good, both for treatment of the primary tumour and for ILND. New strategies for further improvement may be key to ensuring better care in terms of quality and efficacy. These include specific surgical training and the formation of super-regional networks with a multidisciplinary approach that will likely favour high-volume centres.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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