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ORIGINAL ARTICLE

Adherence to EAU guidelines on penile cancer translates into better outcomes: a multicenter international study

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Abstract

Introduction We aimed to evaluate adherence to the EAU guidelines (GL) on penile cancer (PC) with regard to primary surgical treatment and management of lymph nodes and to estimate the influence of adherence to GL on clinical outcome.

Materials and methods This is a retrospective multicenter study (PEnile Cancer ADherence study, PECAD Study) on PC patients treated at 12 European and American centers between 2010 and 2016. Adherence to the EAU GL on the surgical management of the primary penile tumor and lymphadenectomy was evaluated. Descriptive analyses were performed, and survival curves were estimated.

Results Data on 425 patients were considered for the analysis. The EAU GL on surgical treatment of the primary tumor and lymphadenectomy were respected in 74.8% and 73.7% of cases, respectively. Survival analysis showed that adherence to the GL on primary penile surgery was significantly associated with a good overall survival [adjusted HR 0.40 (95% CI 0.20–0.83, p value = 0.014)]. Also, the adherence to the GL on lymphadenectomy was statistically significantly associated with overall survival [adjusted HR 0.48 (95% CI 0.24–0.96, p value = 0.038)]. Limited follow-up and retrospective design represent limitations of this study.

Conclusions Our findings suggest that there is a good adherence to the EAU GL on PC. However, this should be further reinforced, endorsed and encouraged as it might translate into better clinical outcomes for PC patients.

Keywords Penile cancer · Guidelines · Lymphadenectomy · Partial penectomy · Total penile amputation · Survival

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Introduction

Penile cancer (PC), with squamous cell carcinoma accounting for more than 95% of cases, is a rare malignancy with an incidence ranging from 0.6 to 6.8 per 100,000 men [1, 2], accounting for an estimated 0.2–0.4% of malignancies in men [3]. PC is curable in over 80% of cases although survival rates become worse and prognosis poorer in cases of metastatic disease. Survival strongly depends on the staging and management of loco-regional lymph node disease [4], with node-positive patients showing 5-year survival rates ranging from 20 to 80% [5].

The optimal treatment of the primary penile lesion depends on its size, location and feasibility of oncological safety in preserving as much of the organ as possible [penile sparing surgery (PSS)] [6–11]. The risk of occult metastatic disease to the lymph nodes (LN) ranges from not negligible (9%) to significant (23%) in intermediate risk and high-risk clinically node-negative patients [12, 13]. Considering the poor results of systemic treatment for locally advanced PC, bilateral lymph node dissection (LND) or dynamic sentinel biopsy is recommended for patients without palpable inguinal LN [6, 8] in the light of an optimal diagnostic accuracy and potential therapeutic implications [14–16].

However, real life studies have shown that the recommendations for, potentially curative, inguinal LND in high-risk cancer have not been followed [17]. A recent study showed that only about a quarter (26.5%) of the eligible patient received inguinal LND, although the ones that do show an overall better 5-year survival rate [18]. Another study using the SEER database demonstrated that even in those patients who do receive LND, the number of removed LN is inadequate [16]. Adherence to guidelines (GL) for cancer treatment which has been shown to vary significantly between cancer types (54–99%) confirming that guidelines are not gospel and adherence to them depends upon surgeon's experience and patient's preferences [19].

The aim of this study is to evaluate how closely management of the primary penile tumor and regional LN in patients with PC is aligned with the EAU GL and to estimate the association between the adherence to the GL and survival outcomes.

Materials and methods

Study design

Following approval by the local ethics committees, we retrospectively reviewed the clinical notes of all patients with PC that underwent surgical treatment in 12 European and American Centers from 2010 to 2016 (PEnile Cancer ADherence study, PECAD Study).

Demographics, patient's comorbidities, history of circumcision, site and size of the primary lesion and primary local therapy, LN management and histopathology data were collected and analyzed. The type of surgical procedure was decided based on surgeon's and patient's preferences. No perioperative chemotherapy or post-operative radiation was used for the management of the penile lesions. Staging was performed using physical examination and cross-sectional imaging with CT and/or MRI.

Histopathological reports were provided by local genitourinary pathologists and according to local institutional protocol and the AJCC/UICC 2009 TNM Classification for stage and grade. Only squamous cell carcinoma cases were considered.

Follow-up was done with periodical physical examination and imaging according to stage and risk stratification for all patients, and updated by telephone interviews.

"Adherence" to the EAU GL [6] about surgical treatment of the primary lesion and management of the LN was evaluated for all cases. A case was considered "adherent" when the surgical approach was in alignment with the EAU GL or "non-adherent" if the GL were not adhered to. For "non-adherent" cases, an analysis of the reasons for the discrepancies was done and listed as: patient preferences, surgeon's choice and others.

Statistical analysis

Continuous variables were reported as mean and standard deviation (SD), and compared with Student's *t* test. Categorical variables were expressed as absolute number and percent, and analyzed by Chi-square test. Endpoints of survival analysis were cancer progression and overall mortality. Cancer progression was defined as the appearance of local or distant clinical or radiological relapse. Overall mortality was calculated from the time of surgery to death or censored at the date of most recent follow-up for patients who did not die.

Median follow-up and the corresponding interquartile range (IQR) were estimated by the inverse Kaplan–Meier approach. Survival curves were estimated by the product-limit method of Kaplan–Meier and compared by the log-rank statistic. Cox regression model was used to estimate hazard ratio (HR) and 95% confidence interval (CI). Adjusted HRs for adherence to the EAU GL on surgical treatment of the primary tumor were estimated from Cox regression models that included also age, stage pT and lymphadenectomy; while, adjusted HRs for adherence to the EAU GL on LDN were estimated from Cox regression models that included also age, stage pT and grade. Two sensitivity analyses were

performed on the association between adherence to the EAU GL and overall survival. Two sensitivities were performed, the first including in the Cox regression models also multiple comorbidities as covariate, the second excluding from the analysis subjects with multiple comorbidities. A two-tailed p value < 0.05 was considered significant. Data were analyzed using SAS version 9.4 (SAS Inc, Cary, NC, USA).

Results

Patient's demographics, surgical data, and histopathological findings are shown in Table 1. Overall, 425 patients (mean age 65 ± 13) were included in the study. Most of the lesions were located at the prepuce (65.2%). The surgical procedure most commonly performed was partial penectomy (48%) followed by local excision (22.8%). Most patients were at pT1 (30.1%) and pT2 stages (33.2%), with R0 status in > 90% of cases.

At presentation, 244 patients (58%) had palpable inguinal LN. Inguinal LND was performed in 232 (54.6%) patients. Pathological examination of the excised nodes (available for 229 patients) revealed nodal status of pN0 in 41.6%, pN1 in 20.1% and pN2–3 in 38.4% of patients.

The EAU GL regarding treatment of the primary tumor were followed in 74.8% of cases. In cases deemed to be non-adherent the reasons for not following the GL were patient's choice in 12.2%, surgeon's choice in 36.5% and "other reasons" in 20.6% while for the remaining 30.8% of cases no information was available (Fig. 1). Univariate analysis showed that adherence to the GL regarding treatment of the primary lesion increased with advanced disease stage ($p < 0.001$) (Table 2).

The EAU GL for LND were respected in 73.7% of cases (Fig. 1). In non-adherent cases the reasons for not following the GL were patient's choice in 34%, surgeon's choice in 18.8%, "other reasons" in 22.2% (Table 3; Fig. 1). Univariate analysis showed that adherence to the GL regarding management of the LN was better in cases with palpable LN and advanced grade of the primary PC ($p < 0.001$) (Table 3).

Number of comorbidities was not associated with adherence to the EAU GL on primary tumor treatment ($p = 0.741$, Table 2), while a significant association was found with adherence to the EAU GL on LND ($p = 0.003$, Table 3).

At a median follow-up of 17 months (IQR 8–38), 107 patients experienced disease progression, while 36 died from all causes. Progression-free survival (PFS) was not associated with both adherence to the EAU GL on both primary tumor treatment (log-rank p value = 0.548) and LND (log-rank p value = 0.319) (Fig. 2a, b). Adjusted HRs from Cox regression models confirmed these results (Fig. 2a, b) for both adherence to the EAU GL on both primary tumor treatment (HR 1.18, 95% CI 0.73–1.92, p value = 0.504) and LND (HR 0.95, 95% CI 0.56–1.63, p value = 0.862). However, the survival curves showed a significant positive influence on overall survival of adherence to the EAU GL on surgical treatment of the primary tumor (log-rank p value = 0.020) and adherence to the EAU GL on LND management (log-rank p value = 0.020) (Fig. 3a, b). Adjusted

Table 1 Patient demographics, clinical, surgical and pathological characteristics ($n = 425$)

	N	%
Age, years	65.1 (13.2)	
Uncircumcised (missing = 14)	242	41.1
Site of lesion		
Prepuce	277	65.2
Glans	45	10.6
Both	103	24.2
Size of lesion, cm	3.3 (1.8)	
Palpable inguinal nodes (missing = 7)	244	58.4
Stage pT		
< pT1 (including PeIN, Tis, Ta)	61	14.4
T1	128	30.1
T2	141	33.2
T3–T4	95	22.4
Grade (missing = 21)		
G1	120	29.7
G2	205	50.7
G3	79	19.6
Vascular invasion (missing = 62)	68	18.7
Lymphovascular invasion (missing = 62)	84	23.1
Surgical margins (missing = 8)		
R0	379	90.9
R1	38	9.1
Comorbidities (missing = 36)		
No	121	31.1
Diabetes	44	11.3
Hypertension	90	23.1
Cardiovascular disease	21	5.4
Dyslipidemia	8	2.1
Multiple comorbidities	105	27.0
Type of surgery		
Circumcision	27	6.4
Local excision	97	22.8
Glansectomy	40	9.4
Partial penectomy	204	48.0
Total penectomy	57	13.4
Lymphadenectomy	232	54.6
Nodal status (missing = 13)		
pN0	91	41.6
pN1	44	20.1
pN2–3	84	38.4

Values expressed as *n* (%) or mean (SD)

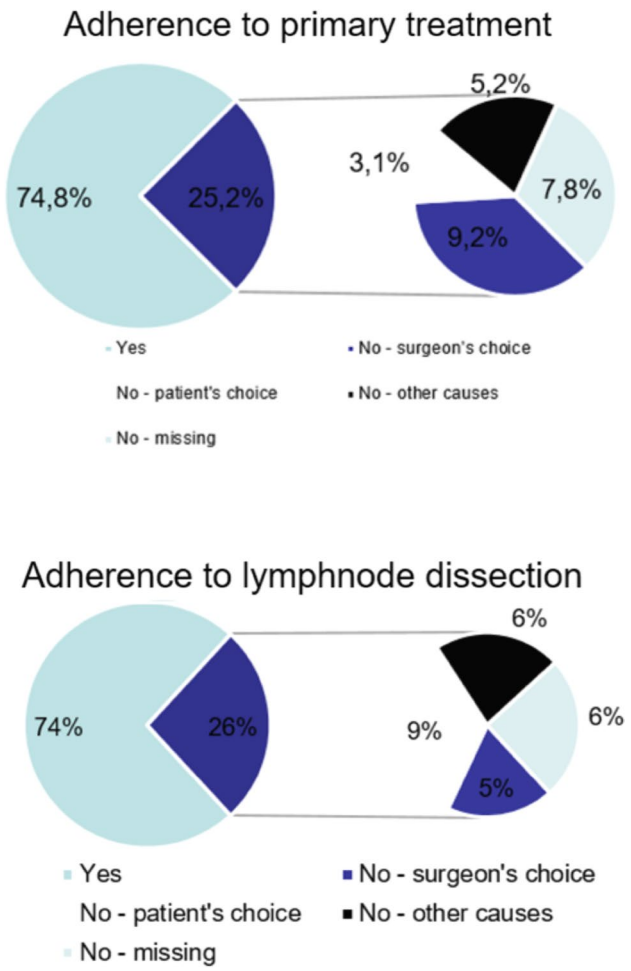

Fig. 1 Pie in pie graphs depicting the adherences rate and the reasons for non-adherence for primary treatment (**a**) and lymph node dissection (**b**)

HRs from Cox regression models confirmed these results for both adherence to the EAU GL on both primary tumor treatment (HR 0.40, 95% CI 0.20–0.83, p value = 0.014) and LND (HR 0.48, 95% CI 0.24–0.96, p value = 0.038) (Fig. 3a, b). In the first sensitivity analysis (including in the Cox regression model also multiple comorbidities) previous results were confirmed for both adherence to the EAU GL on both primary tumor treatment (HR 0.41, 95% CI 0.20–0.84, p value = 0.015) and LND (HR 0.49, 95% CI 0.25–0.99, p value = 0.047). In the second sensitivity analysis (excluding subjects with multiple comorbidities) previous associations were also confirmed (data not shown).

Discussion

The first EAU GL on PC were published in 2000 (last updated in 2014) [6]. The goal of this study was to assess the adherence to the EAU GL regarding management of primary lesion and regional LN across institutions worldwide, and the correlation between adherence to GL and clinical outcomes.

Although urologists are familiar with the EAU GL, adherence to the GL remains a challenge. Due to the rarity of the PC, GL are based on small number and/or methodologically weak publications that result in low level of evidence, weak degrees of recommendation and consequently limited adoption of the GL itself. Physicians are, not surprisingly, more likely to follow GL on topics with which they feel more familiar and PC is certainly not the topic most urologists are more familiar with [20].

PC has some characteristics that should be highlighted. The best chances of cure are usually achieved with surgery, whereas PC is a highly emotive disease where patients are actively involved in decision-making. This is due to the fact that decisions about surgical treatment (e.g. total penectomy) can bare devastating consequences to the quality of life and mental well-being [21]. The patient's extent of involvement in decision-making is difficult to capture within a clinical study; however, it undoubtedly influences the outcome. Our data showed a wider discrepancy between GL and clinical practice in localized tumors that should be ideally treated with PSS.

In our study, treatment of the primary PC was aligned with the EAU GL in approximately 75% of cases. This is in line with results from a Swedish study showing an adherence rate to the EAU GL of 71% for < T2 stage PC [11]. A recent US study on 6396 patients showed that the National Comprehensive Cancer Network (NCCN) GL for the management of the primary tumor were followed in 91.4–96.6% of cases depending on the stage [22]. However, those results represent US practice patterns already in use before the introduction of the NCCN GL and, therefore, do not reflect actual adherence to the GL.

In our study, tumor stage was the sole significant factor associated with adherence to the GL regarding management of the primary PC ($p < 0.001$). This finding might mean that we are still treating smaller penile tumors with more radical surgery than necessary. There is a strong evidence that PSS can be safely recommended in < T2 stage and low-grade PC [23, 24]. Despite the paradigm shift to PSS, some centers, probably because of limited experience in PC surgery continue to adopt a more radical approach not adherent to the recommendations of the latest GL. Increased experience and/or centralization of PC treatment are keys to the wider and safer use of PSS in selected cases.

Staging and management of LN disease is one of the most important prognostic indicators of survival in PC. The EAU GL suggest LND or sentinel node biopsy in cN0 patients with pT1b, T2–T4, and in all cases of cN1/cN2 [6] given the strong evidence in terms of cancer-specific survival following extensive LND [14, 16]. However, in practice only a

Table 2 Patient characteristics by adherence to primary treatment

	Adherence to primary treatment				*p* value
	No ($n=107$)		Yes ($n=318$)		
	N	%	*N*	%	
Age, years	66.6 (13.6)		64.6 (13.0)		0.176
Uncircumcised (missing = 14)	55	55	187	60.1	0.365
Site of lesion					0.481
Prepuce	72	67.3	205	64.5	
Glans	8	7.5	37	11.6	
Both	27	25.2	76	23.9	
Size of lesion, cm	3.3 (1.9)		3.3 (1.7)		0.923
Palpable lymph nodes (missing = 7)	55	52.4	189	60.4	0.150
Stage pT					< 0.001
< pT1 (including PeIN, Tis, Ta)	23	21.5	38	12.0	
T1	44	41.1	84	26.4	
T2	25	23.4	116	36.5	
T3–T4	15	14.0	80	25.2	
Grading (missing = 21)					0.060
G1	40	37.7	80	26.9	
G2	44	41.5	161	54.0	
G3	22	20.8	57	19.1	
Vascular invasion (missing = 62)	13	13.3	55	20.8	0.105
Lymphovascular invasion (missing = 62)	24	24	60	22.8	0.811
Surgical margins (missing = 8)					0.495
R0	99	92.5	280	90.3	
R1	8	7.5	30	9.7	
Comorbidities (missing = 36)					0.687
No	33	33.7	88	30.2	
Diabetes	13	13.3	31	10.7	
Hypertension	18	18.4	72	24.7	
Cardiovascular disease	4	4.1	17	5.8	
Dyslipidemia	3	3.1	5	1.7	
Multiple comorbidities	27	27.6	78	26.8	
Number of comorbidities (missing = 36)					0.741
0	33	33.7	88	30.2	
1	38	38.8	125	43.0	
> 1	27	27.6	78	26.8	
Type of surgery					0.054
Circumcision	4	3.7	23	7.2	
Local excision	21	19.6	76	23.9	
Glansectomy	10	9.4	30	9.4	
Partial penectomy	49	45.8	155	48.7	
Total penectomy	23	21.5	34	10.7	
Lymphadenectomy	48	44.9	184	57.9	0.020
Nodal status (missing = 13)					0.970
pN0	19	40.4	72	41.9	
pN1	10	21.3	34	19.8	
pN2–3	18	38.3	66	38.4	

Values expressed as *n* (%) or mean (SD)

Table 3 Patient characteristics by adherence to lymphadenectomy

	Adherence to lymphadenectomy				*p* value
	No ($n=110$)		Yes ($n=312$)		
	N	%	*N*	%	
Age, years	67.4 (13.1)		64.4 (13.1)		0.038
Uncircumcised (missing = 14)	67	63.8	175	57.2	0.234
Site of lesion					< 0.001
Prepuce	52	46.4	225	71.9	
Glans	17	15.2	28	9.0	
Both	43	38.4	60	19.2	
Size of lesion, cm, mean	3.5 (2.1)		3.2 (1.6)		0.302
Palpable lymph nodes (missing = 7)	42	38.5	202	65.4	< 0.001
Stage pT					0.027
< pT1 (including PeIN, Tis, Ta)	8	7.1	53	16.9	
T1	40	35.7	88	28.1	
T2	43	38.4	98	31.3	
T3–T4	21	18.8	74	23.6	
Grading (missing = 21)					< 0.001
G1	37	33.3	83	28.3	
G2	66	59.5	139	47.4	
G3	8	7.2	71	24.2	
Vascular invasion (missing = 62)	19	19.6	49	18.4	0.801
Lymphovascular invasion (missing = 62)	23	22.8	61	23.3	0.918
Surgical margins (missing = 8)					0.397
R0	104	92.9	275	90.2	
R1	8	7.1	30	9.8	
Comorbidities (missing = 36)					0.025
No	20	19.1	101	35.6	
Diabetes	14	13.3	30	10.6	
Hypertension	27	25.7	63	22.2	
Cardiovascular disease	4	3.8	17	6.0	
Dyslipidemia	2	1.9	6	2.1	
Multiple comorbidities	38	36.2	67	23.6	
Number of comorbidities (missing = 36)					0.003
0	20	19.1	101	35.6	
1	47	44.8	116	40.9	
> 1	38	36.2	67	23.6	
Type of surgery					0.026
Circumcision	11	9.8	16	5.1	
Local excision	14	12.5	83	26.5	
Glansectomy	12	10.7	28	9.0	
Partial penectomy	58	51.8	146	46.7	
Total penectomy	17	15.2	40	12.8	
Nodal status (missing = 13)					0.029
pN0	15	65.2	76	38.8	
pN1	1	4.4	43	21.9	
pN2–3	7	30.4	77	39.3	

Table values are *n* and % or mean and standard deviation (SD)

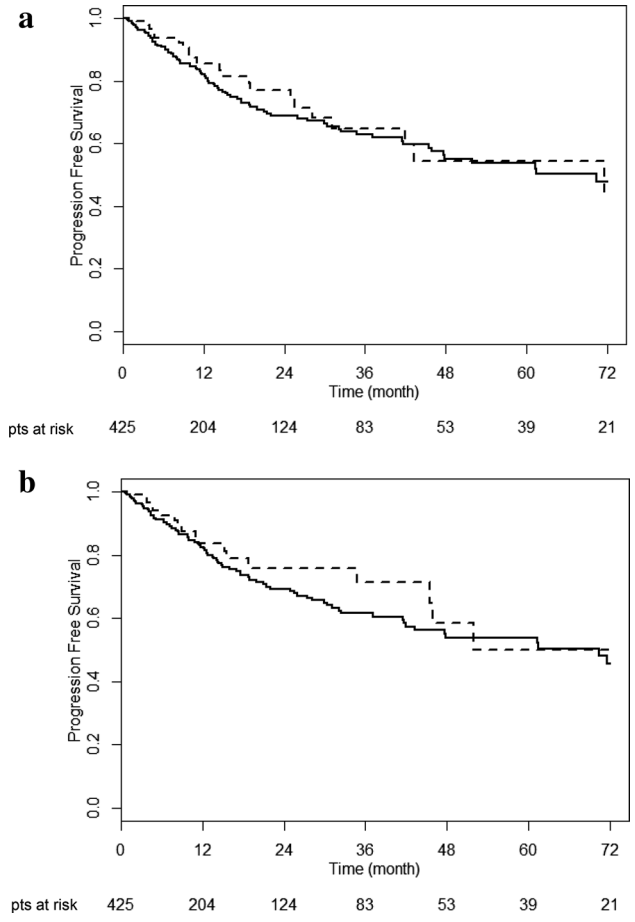

Fig. 2 Progression-free survival by adherence to primary treatment (**a**) and to lymph node dissection (**b**). Solid line: adherent cases; dotted line: non-adherent cases

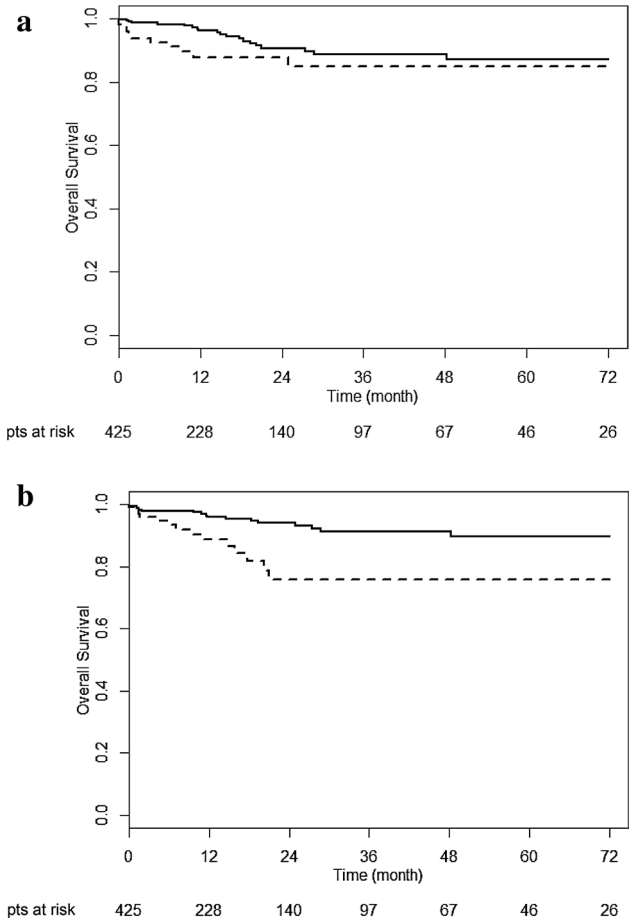

Fig. 3 Overall survival by adherence to primary treatment (**a**) and to lymph node dissection (**b**). Solid line: adherent cases; dotted line: non-adherent cases

proportion of patients who should undergo LND are in fact treated with LND. Reasons for this discrepancy should probably be sought in the reality that LND can be a challenging procedure with significant mortality and morbidity.

Adherence to GL on LND in PC has historically been suboptimal. Thuret queried the SEER database from 1988 to 2006 looking into the adherence rates to the National Cancer Institute (NCI) recommendations regarding LND in high grade and stage PC [25]. He found that only 27.6% of T1 high grade and T2–4 PCs had undergone a LND. Multivariate analysis showed that the rate of LND was directly proportional to T stage but adversely related to advanced patient age. There was also an observed increase in LND rates over time, which is also reflected in more recent studies [25].

A US study showed that 62.9% of patients with cN1–cN2 disease underwent regional LND [22] in contrast to the NCCN GL. A recent study on 1123 PC patients with positive LN showed that 66.8% of patients received LND [17]. In the Swedish PC study only 50% of the patients with > pT1G2 disease was managed according to GL regarding LN staging. In the same study 74% of men with cN1–3 tumors underwent LND [11]. Our study showed that 58.4% of patients had palpable LN while overall 54.6% of patients underwent LND, a rate consistent with other studies with LND rates ranging from 36.8 to 74%, for all stages [11, 22, 26].

In our study the EAU GL on LN management were respected in 73.7% of cases with analysis showing better adherence to the GL in cases with palpable LN and advanced grade of the primary tumor. Interestingly, in our study, age was not among the parameters related to the adherence to the GL on LND.

Our study showed that GL on both primary tumor treatment and LN surgical management are equally respected in most patients and that adherence has increased compared to previous studies. The improved adherence to the GL can be attributed to wider dissemination, and adoption of the GL and increased awareness of the importance of LND.

The reasons for not performing LND when indicated were not assessed, as was the non-homogenous use of dynamic sentinel node biopsy. Some patients might have

received alternative treatments, such as radiation therapy of the LN, while others might have had considered to harbor unresectable LN disease. However, looking into the reasons for non-adherence to the GL, it is clear that patient's preference (34%) had the strongest impact in not following the GL on LN management, whereas on the contrary the surgeon's choice prevailed in the management of the primary penile tumor (36.5%). One would expect the opposite, that patients would be more involved in decision-making regarding the surgical management of the PC. It is logical, however, to assume that some patients would be either reluctant or not deemed medically fit to proceed with surgery given that radical inguinal lymphadenectomy is high-risk surgery with an estimated complication rate more than 50% [27, 28].

Adherence to GL is better in advanced and high-risk disease, which is reasonable. Non-adherence to GL in our study could be attributed to the heterogeneous surgical expertise of the different centers regarding LND and to practical constraints like the non-ubiquitous availability of the sentinel biopsy.

Despite the short follow-up, our study suggests a positive impact of adherence to GL and clinical outcome of PC patients. Two recent studies have shown that survival is significantly better in patients with node-positive PC which receive LND [17], and that cause-specific survival is better in patients who received an extensive LND [16].

Our study is certainly not devoid of limitations. First and foremost, the limited median follow-up does not allow to draw definitive conclusions on the association between adherence to guideline and better survival. Moreover, the study data derives from a very heterogenous group of PC patients treated at 12 different institutions with relevant differences in terms of disease progression definition, and varying degrees of specialization and surgical skills ranging from community hospitals to tertiary referral centers. The use of dynamic sentinel node biopsy was routinely adopted in just a few centers and was not considered relevant for the main aims of the study. Moreover, we did not have specific information regarding the lymphadenectomy techniques used at each center (standard versus modified). This can be regarded as another limitation. On the other hand, as with all multicenter and retrospective studies there is the advantage of increased generalizability of the results as more the surgeons and clinical sites participating, the more applicable to the general patient populations the results of the study should be. The lack of central pathology review might represent another drawback, with a presumed higher accuracy of pathologically assessed variables, nevertheless it is noteworthy that none of the previously reported multi-institutional studies relied on central pathology [29]. As previously discussed, the degree of patient involvement in decision-making and hence adherence to the GL regarding surgical treatment may have also influenced the results, however it cannot be captured in this study.

The present study highlights a problem the urological community is faced with; the gap between scientific evidence and clinical practice. The suboptimal adherence to the GL on PC underscores the need for action to facilitate dissemination and adoption of GL. The EAU has recently taken steps to tackle the problem of discordant guideline adherence by launching the "IMAGINE" project (Impact Assessment of GL Implementation and Education) with the scopes of evaluating the impact of the EAU GL and elucidating the barriers thereby optimizing adherence, with the ultimate goal of improving patient care [30].

Conclusions

Our study suggests that adherence to the EAU GL on PC in different geographical regions of the world is above 70% for both the treatment of primary tumor and the LNs management. Although encouraging, these figures are still suboptimal as adherence to GL might translate into better clinical outcomes. Thus, strategies to improve adherence to GL should be further reinforced, endorsed and encouraged.

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