



Adherence to the EAU guideline recommendations for systemic chemotherapy in penile cancer: results of the E-PROPS study group survey

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Abstract

Objectives To validate the adherence of urologists to chemotherapy recommendations given in the EAU guidelines on PeCa. The European Association of Urology (EAU) guidelines on penile cancer (PeCa) are predominantly based on retrospective studies with low level of evidence.

Materials and methods A 14-item-survey addressing general issues of PeCa treatment was developed and sent to 45 European hospitals. 557 urologists participated in the survey of which 43.5%, 19.3%, and 37.2% were in-training, certified, and in leading positions, respectively. Median response rate among participating departments was 85.7% (IQR 75–94%). Three of 14 questions addressed clinical decisions on neoadjuvant, adjuvant, and palliative chemotherapy. Survey results were analyzed by bootstrap-adjusted multivariate logistic-regression-analysis to identify predictors for chemotherapy recommendations consistent with the guidelines.

Results Neoadjuvant, adjuvant, and palliative chemotherapy was recommended according to EAU guidelines in 21%, 26%, and 48%, respectively. For neoadjuvant chemotherapy, urologists holding leading positions or performing chemotherapy were more likely to recommend guideline-consistent treatment (OR 1.85 and 1.92 with $p_{(\text{bootstrap})} = 0.007$ and 0.003 , respectively). Supporting resources (i.e., guidelines, textbooks) were used by 23% of survey participants and significantly improved consistency between treatment recommendations and Guideline recommendations in all chemotherapy settings ($p_{(\text{bootstrap})} = 0.010$ – 0.001). Department size and university center status were no significant predictors for all three endpoints.

Conclusions In this study, we found a very low rate of adherence to the EAU guidelines on systemic treatment for PeCa. Further investigations are needed to clarify whether this missing adherence is a consequence of limited individual knowledge level or of the low grade of guideline recommendations.

Keywords Guideline compliance · Penile squamous cell carcinoma · Neoadjuvant chemotherapy · Adjuvant chemotherapy · Palliative chemotherapy

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Abbreviations

EAU	European association of urology
IQR	Interquartile range
PeCa	Penile cancer
GoR	Grade of recommendation
SR	Supporting resources
SOP	Standard operating procedure

Introduction

Despite its low incidence rate in European countries (0.45–1.7 per 100,000 men), optimized treatment for advanced penile cancer (PeCa) is critical, as it represents a potential mutilating and life-threatening disease [1]. Evidence-based guidelines recommendations, i.e., the EAU guidelines on penile cancer [2], provide support for individual decision making in advanced PeCa. However, the quality of such has been questioned in recent years [3–5].

Developing recommendations on chemotherapy in PeCa may be biased by various factors. First, due to the rarity of PeCa, recommendations are mainly based on retrospective data with low level of evidence. Existing clinical studies on neoadjuvant and palliative chemotherapy show methodological limitations resulting in a low grade of recommendation (weak GoR) whereas recommendations on adjuvant chemotherapy exhibit a higher GoR based on higher levels of available evidence (strong GoR) [2]. Despite the partly low level of evidence, EAU guidelines on PeCa include all currently available study data. Therefore, these recommendations represent obligatory treatment advices [6–13]. Consequently, better clinical outcomes and a reduced cancer-specific mortality would be expected based on a strong adherence to guidelines [4, 14].

Since PeCa in advanced and metastatic stages is associated with a very low cancer-specific survival, therapeutic decisions should be based on the best available evidence. Therefore, the objective of this study was to assess to which degree decisions on systemic chemotherapy by clinical urologists adhere to the EAU guidelines on PeCa in the neoadjuvant, adjuvant, and palliative setting. Furthermore, we attempted to investigate independent factors resulting in an increased adherence to the EAU guidelines.

Recent publications draw contradictory conclusions concerning the adherence to guidelines recommendations for penile cancer [3–5]. Therefore, three hypotheses were generated for validation. First, we presumed that urologists correctly indicated chemotherapy (neoadjuvant, adjuvant, and palliative) according to the EAU guidelines on penile cancer in more than 60% of our case studies. Second, we assumed that adherence to guideline recommendations was (I) higher for urologists working at university hospitals compared to urologists at non-university hospitals, (II) higher

for urologists performing chemotherapy themselves than for urologists delegating chemotherapy to a department of oncology, (III) higher for urologists in leading positions than for urologists in-training, (IV) higher for urologists using supporting resources (SR) [e.g., guidelines, standard operating procedures (SOPs), medical textbooks] to answer the survey than for urologists not using SR, and (V) directly related to the number of patients with PeCa treated in the given center. Third, urologists' decisions concerning adjuvant chemotherapy adhere better to the EAU guidelines than decisions concerning palliative and neoadjuvant chemotherapy, given the higher grade of recommendations for adjuvant chemotherapy within these guidelines. Evaluation of these hypotheses were conducted based on a survey created by the European PROspective Penile Cancer Study group (E-PROPS).

Materials and methods

E-PROPS was initiated to evaluate therapeutic management of PeCa patients in three consecutive modules. Module 1 contains a survey answered by clinical urologists from various departments in Europe. Module 2 will be a retrospective multicenter study about PeCa patients treated in the past 10 years. Finally, module 3 will represent a prospective multicenter study on PeCa patients including a tissue and serum database. The first module comprised 45 urological departments in four European countries (Germany, Switzerland, Austria, and Italy), who were willing to participate in the E-PROPS study group. The German-language survey was established by the E-PROPS' steering-committee and consisted of 14 questions addressing the following aspects: (I) position of the surveyed person in the urological clinic, (II) personal responsibilities in PeCa therapy management, (III) individual knowledge on therapeutic strategies, (IV) therapeutic management of PeCa patients (primary surgery, lymphadenectomy, chemotherapy) in the given urological department as well as (V) the use of SR for answering the survey. Three of these 14 questions were specifically addressing systemic chemotherapy. In addition, the following parameters were collected from the participating departments: (I) status of the center (university vs. non-university), (II) department responsible for performing chemotherapy (urology vs. oncology), (III) size of the urological department, (IV) number of PeCa patients treated in the urological department in 2017. The comprehensibility of the survey's content was evaluated in detail by structured interviews with ten non-participating urologists of different clinical experience levels. Establishment, analysis, and interpretation of the survey were carried out in accordance to the STROBE-criteria [15].

The survey, its application, and the recruitment letter were presented to the Institutional Review Board at the University of Regensburg and the project was granted exempt status. In Q3/2018 the survey was sent to 681 urologists at the 45 participating departments in four countries where urologists predominantly or partly conduct also systemic tumor treatment. The benchmark for a completed survey to be included in the evaluation was an at least 92% availability of results of evaluable items per survey (13 of the 14 items had to be checked). Nine of the 566 returned surveys failed this benchmark and were excluded. Thus, a total number of 557 surveys were finally analyzed. Among participating centers, the median response rate was 85.7% (IQR 75–94%).

The indication for chemotherapy according to the EAU guidelines on PeCa was evaluated separately for each clinical setting (neoadjuvant, adjuvant, palliative). Accordingly, urologists were asked to specify the tumor stage for which they would indicate neoadjuvant, adjuvant or palliative chemotherapy (Fig. 1).

The following variables (predictors) were defined: “employed at a university hospital” (yes or no), “size of department” (continuously coded based on number of patient capacity/beds), “leading position” (senior or head physician vs. other), “urologists performing chemotherapy themselves” (vs. oncologists exclusively performing chemotherapy), “number of patients with PeCa treated in 2017”

Fig. 1 Specific questions regarding chemotherapy in patients with PeCa, multiple answers were allowed. Correct indications according to the EAU guidelines are highlighted in green [16]

Specific questions about chemotherapy in patients with PeCa	
Question 1	At which disease stage would you perform neoadjuvant chemotherapy?
option 1	cT3cN0
option 2	cT4cN0
option 3	pT3cN2
option 4	pT3cN3
option 5	I'm not sure
Question 2	At which disease stage would you perform adjuvant chemotherapy?
option 1	pT3pN0
option 2	pT3pN1
option 3	pT3pN2
option 4	pT3pN3
option 5	I'm not sure
Question 3	At which stage would you perform palliative chemotherapy?
option 1	pT3cN2M0
option 2	pT3cN3M0
option 3	pT3pN1M1
option 4	pT3pN2M1
option 5	I'm not sure

(cont.), “use of SR for answering the survey (e.g., guidelines, standard-operating-procedures/SOPs)” (yes or no). A correct recommendation on chemotherapy according to the EAU guidelines on PeCa (2014 update) was defined as the endpoint [16]. Categorical variables were compared using Fisher’s exact test (2×2).

Independent predictive criteria for guideline-adherent treatment recommendations were analyzed by three separate multivariate logistic regression analyses. The internal validity of the prediction models was evaluated by bootstrapping with 1000 re-samples.

Statistical analyses were performed using IBM SPSS®V25 (Armonk, USA). Reported p values are two-sided with the statistical significance level set at $p < 0.05$.

Results

Detailed characteristics of the 45 participating centers are presented in Table 1. A median number of five PeCa patients (IQR 3–8) was treated in 2017 per department. Urologists performed 35.6% (16/45 departments) of chemotherapy regimens exclusively, and 24.4% (11/45 departments) of chemotherapy regimens were performed in collaboration with the respective department of oncology. 19/45 (42.2%) of the participating urological departments were university centers. 43.5%, 19.3%, and 37.2% of the responding urologists were in-training, certified, and in leading positions, respectively. 23.3% used SR to answer the survey (Table 2).

A descriptive analysis of the answers to the questionnaire regarding neoadjuvant, adjuvant, and palliative chemotherapy is displayed in Table 2. 117 (21%) urologists recommended neoadjuvant chemotherapy according to the guidelines, 142 (25.5%) urologists recommended a guideline-conform adjuvant chemotherapy, and almost half of all

participating urologists ($n = 265$, 47.6%) recommended a palliative chemotherapy in accordance with the guidelines. Overall, 31.3% of all recommendations on systemic chemotherapy were adherent to the EAU guidelines. The use of SR significantly improved the adherence of treatment recommendations to the guidelines in all three settings (28.9% with SR vs. 18.5% without SR, $p = 0.013$; 57% with SR vs. 16.2% without SR, $p < 0.001$; 65.6% with SR vs. 42.8% without SR, $p < 0.001$; for neoadjuvant, adjuvant, and palliative therapy, respectively).

Results of the multivariate logistic regression analyses are presented in Table 3. Significant predictors for guideline-adherent recommendations concerning neoadjuvant chemotherapy were the variables “leading position” (OR 1.85, $p_{(\text{bootstrap})} = 0.007$), “urologists performing chemotherapy themselves” (OR 1.92, $p_{(\text{bootstrap})} = 0.003$) and “use of SR for completing the questionnaire” (OR 1.88, $p_{(\text{bootstrap})} = 0.010$). Significant predictors for a therapy decision according to EAU guidelines regarding adjuvant chemotherapy were the variables “number of patients with PeCa treated in 2017” (OR 1.05, $p_{(\text{bootstrap})} = 0.009$) and “use of SR for completing the questionnaire” (OR 6.9, $p_{(\text{bootstrap})} = 0.001$). The only significant predictor for a recommendation consistent with the guidelines for palliative chemotherapy was “use of SR for completing the questionnaire” (OR 2.61, $p_{(\text{bootstrap})} = 0.001$).

Both department size and university status had no significant impact on all three endpoints (Table 3).

Discussion

The present study is the first international survey evaluating the preference of chemotherapy management for patients with high-risk PeCa among urologists in Europe and their adherence to EAU guidelines.

Table 1 Characteristics of 45 participating centers within the E-PROPS study group

Criterion	<i>n</i>
Country of the department	
Germany	34 (75.6%)
Austria	8 (17.8%)
Switzerland	2 (4.4%)
Italy	1 (2.2%)
Number of university centers	19 (42.2%)
Median number of urologists per center (IQR)	14 (10–18)
Median number of in-house patient capacity (beds) per department (IQR)	39 (30–50)
Median number of patients with PeCa treated in 2017 in each urological department (IQR), $n = 45$	5 (3–8)
Departments performing chemotherapy for patients with PeCa	
Exclusively urological department	16 (35.6%)
Urological and oncological department	11 (24.4%)
Exclusively oncological department	18 (40%)

Table 2 Descriptive analysis of the study population and the answers to the questionnaire regarding neoadjuvant, adjuvant, and palliative chemotherapy

Criterion	<i>n</i> (%)
Professional status <i>n</i> = 554	
Resident	241 (43.5)
Board certified urologist	107 (19.3)
Leading position (senior consultant or senior physician)	206 (37.2)
Indication for neoadjuvant chemotherapy, <i>n</i> = 557	
Answer category 1: option 1 (cT3cN0) only	27 (4.8)
Answer category 2: option 2 (cT4cN0) only	23 (4.1)
Answer category 3: option 3 (pT3cN2) only	37 (6.8)
<i>Answer category 4: option 4 (pT3cN3; fixed lymph nodes) only</i>	<i>117 (21)</i>
Answer category 5: option 5 (uncertain)	105 (18.9)
Answer category 6: combinations of options including option 4	217 (39)
Answer category 7: combinations of options without option 4	31 (5.6)
Indication for adjuvant chemotherapy, <i>n</i> = 557	
Answer category 1: option 1 (pT3pN0) only	22 (3.9)
Answer category 2: option 2 (pT3pN1) only	81 (14.5)
Answer category 3: option 3 (pT3pN2) only	35 (6.3)
Answer category 4: option 4 (pT3pN3) only	18 (3.2)
Answer category 5: option 5 (uncertain)	75 (13.5)
<i>Answer category 6: combination of option 3 and option 4</i>	<i>142 (25.5)</i>
Answer category 7: combinations of options including answer category 6	162 (29.1)
Answer category 8: combinations of options without answer category 6	22 (3.9)
Indication for palliative chemotherapy, <i>n</i> = 557	
Answer category 1: option 1 (pT3cN2M0)	7 (1.3)
Answer category 2: option 2 (pT3cN3M0)	3 (0.5)
Answer category 3: option 3 (pT3pN1M1)	115 (20.6)
Answer category 4: option 4 (pT3pN2M1)	35 (6.3)
Answer category 5: option 5 (uncertain)	84 (15.1)
<i>Answer category 6: combination of option 3 and option 4</i>	<i>265 (47.6)</i>
Answer category 7: combination of options including answer category 6	40 (7.2)
Answer category 8: combination of options without answer category 6	8 (1.4)
Use of supporting resources (e.g., guidelines), <i>n</i> = 549	128 (23.3)

Correct answers according to the EAU guidelines are highlighted in italics

First, we hypothesized that 60% of chemotherapy recommendations for PeCa were in line with the EAU guidelines for each therapeutic setting. However, only 21.0%, 25.5%, and 47.6% of the participating urologists recommended a chemotherapy regime consistent with EAU guidelines in the neoadjuvant, adjuvant, and palliative setting, respectively. Second, we hypothesized that adherence to guidelines in all settings was higher for urologists at university centers, performing chemotherapy themselves, holding leading positions and/or using SR for completing the survey. In contrast to these hypotheses, only the variable “using SR” was found to be a significant positive predictor for guideline-adherent treatment recommendations in all three therapy settings. Additionally, an independent impact on the endpoint was demonstrated for the variables “performing chemotherapy themselves” and “holding a leading position” in the neoadjuvant setting. Finally, the number of patients with PeCa

treated per year represented a significant predictor for recommendations according to the guidelines in the adjuvant therapy setting. In contrast, no specific impact of the GoR on the extent of guideline adherence was found. The high GoR concerning adjuvant chemotherapy of the EAU guidelines on PeCa did not result in a higher adherence to the guidelines compared to the weaker GoR for the neoadjuvant and palliative setting (rates of adherence: 25.5% vs. 21.0% and 47.6% for adjuvant vs. neoadjuvant and palliative treatments, respectively).

To our knowledge, no comparable studies concerning therapy management in advanced PeCa patients are currently available. Furthermore, retrospective data regarding the guideline-based chemotherapeutic management of patients with PeCa is missing. To date, only three studies have provided retrospective data concerning guideline-adherent primary local treatment and inguinal lymphadenectomy in

Table 3 Bootstrap-adjusted multivariate logistic regression analysis for a correct recommendation concerning neoadjuvant, adjuvant, and palliative chemotherapy for patients with PeCa according to the EAU guidelines [16]

Predictor	OR (95% CI)	<i>p</i>	<i>P</i> _(bootstrap)
Endpoint: correct recommendation on neoadjuvant chemotherapy according to the EAU guidelines			
University centers	0.96 (0.62–1.50)	0.865	0.869
In-house patient capacity per department, cont	1.01 (0.99–1.02)	0.502	0.512
<i>Leading position [senior or head physician] (vs. residents and certified urologists)</i>	<i>1.85 (1.21–2.85)</i>	<i>0.005</i>	<i>0.007</i>
<i>Urologist performing chemotherapy for PeCa patients (vs urologist not performing chemotherapy)</i>	<i>1.92 (1.21–3.03)</i>	<i>0.005</i>	<i>0.003</i>
Number of PeCa patients treated in 2017	1.01 (0.96–1.05)	0.783	0.782
<i>Use of supporting resources for completing the questionnaire</i>	<i>1.88 (1.17–3.04)</i>	<i>0.009</i>	<i>0.010</i>
Endpoint: correct recommendation on adjuvant chemotherapy according to the EAU guidelines			
University centers	0.89 (0.57–1.39)	0.621	0.603
In-house patient capacity per department, cont	0.98 (0.96–1.00)	0.087	0.056
Leading position [senior or head physician] (vs. residents and certified urologists)	1.41 (0.91–2.18)	0.123	0.142
Urologist performing chemotherapy for PeCa patients (vs urologist not performing chemotherapy)	0.86 (0.56–1.35)	0.519	0.474
<i>Number of PeCa patients treated in 2017</i>	<i>1.05 (1.01–1.10)</i>	<i>0.021</i>	<i>0.009</i>
<i>Use of supporting resources for completing the questionnaire</i>	<i>6.90 (4.39–10.84)</i>	<i>< 0.001</i>	<i>0.001</i>
Endpoint: correct recommendation on palliative chemotherapy according to the EAU guidelines			
University centers	0.92 (0.64–1.32)	0.641	0.678
In-house patient capacity per department, cont	1.00 (0.99–1.02)	0.582	0.553
Leading position [senior or head physician] (vs. residents and certified urologists)	1.16 (0.81–1.66)	0.407	0.392
Urologist performing chemotherapy for PeCa patients (vs urologist not performing chemotherapy)	0.98 (0.68–1.40)	0.911	0.911
Number of PeCa patients treated in 2017	1.01 (0.97–1.04)	0.77	0.77
<i>Use of supporting resources for completing the questionnaire</i>	<i>2.61 (1.71–3.99)</i>	<i>< 0.001</i>	<i>0.001</i>

Statistically significant predictors are highlighted in italics

patients with PeCa [3–5]. Bada et al. found an adherence to EAU guideline recommendations of 66% for primary local treatment of PeCa. Furthermore, they demonstrated that guideline-consistent lymphadenectomy was performed in 70% of all retrospectively analyzed PeCa patients [3]. Cindolo et al. showed similar adherence rates for primary local treatment (74.8%) and lymphadenectomy (73.7%) [4]. In contrast, Thuret et al. assessed a low adherence (27.6%) to recommendations of the National Cancer Institute (NCI) concerning lymphadenectomy in patients with PeCa [5]. Reasons for such a non-compliance might be manifold. Thuret et al. pointed out that lacking guideline adherence of local therapy might be caused by surgeon's experience, patient's preference, and the high degree of associated morbidity for some procedures (e.g., wound healing, lymphedema after lymphadenectomy) [5]. Cabana et al. identified other general factors that could result in a low consistency with guidelines, i.e., lack of awareness and missing familiarity with the guideline topic [17]. Concerning the use of SR, our results are in accordance with publications by Cindolo et al., Heins et al., and Breen et al.. These studies have underlined the fact that the use of SR significantly improves adherence to clinical guidelines [4, 14, 18].

In line with the National Institute for Clinical Excellence [19], our results support efforts to predominantly

treat patients with PeCa (and other orphan diseases) within experienced centers, as the adherence to treatment recommendations of pertinent guidelines positively correlates with the number of patients with PeCa treated per year in a given center (at least in the adjuvant setting). We assume that a larger number of treated patients increases the awareness and knowledge of both PeCa treatment in general and corresponding guidelines, with treatment recommendations subsequently better conforming to the latter (although this assumption could only be demonstrated within the adjuvant setting in the present study).

This study has several limitations. At this step of E-PROPS, we can only deliver survey-based data, which are difficult to compare with retrospective studies. Questionnaires are prone to misinterpretation of questions and wrong perception of tasks (e.g., single vs. multiple choice). We tried to diminish this limitation by thorough upfront testing for clarity and comprehensibility of the questionnaire by ten non-participating urologists of different experience levels. In clinical practice, the impact of a treatment decision is much higher than in a survey-questioned case study as such decisions result in a real therapy with possibly significant consequences for the given patient. For this reason, decision making in a real-life setting is associated with more consequences and taken more seriously than participation

in a survey. This might induce judgment differences. The adherence to guidelines in real-life might be much better, especially in times of encouraged interdisciplinarity and constant tumor boards. This assertion is supported by the observation that urologists holding leading positions give correct treatment recommendations according to the guidelines more frequently than urologists in non-leading positions. This might be caused by their responsibility and higher awareness for correct PeCa treatment. Using the survey, individual perspectives of each given urologist were requested. Conversely, in clinical practice, one might assume that treatment decisions are usually based on the expertise of physicians holding senior positions or multidisciplinary tumor boards. Furthermore, reasons for the individual choice of one treatment over another (e.g., patient age, comorbidity and preferences, or experiences of the given center) were not investigated in any of the three clinical cases (neoadjuvant, adjuvant, palliative) of our survey. In real life, as reflected by retrospective analyses, this fact may influence decision making in a significant manner. Contrary to the STROBE criteria, we do not present criteria of the non-responders as the survey was answered anonymously [15]. Besides this restriction, the rest of STROBE criteria were met. Furthermore, we only focused on urologists and did not include medical oncologists to avoid a potential bias introduced by medical specialties. Moreover, in multivariate regression analyses, an adjustment to the number of urologists per center could not be implemented due to high collinearity with the status of the center (university vs. non-university). Despite the limitations of survey-based analyses, the present study shows an exceptionally high response rate of 85.7%—with three quarters of participating centers reaching response rates of $\geq 75\%$. Therefore, the present study seems to representatively reflect clinical practice concerning chemotherapy in patients with PeCa across German-speaking parts of Europe. With 75.6% of the 45 participating centers located in Germany, chemotherapy recommendations for patients with PeCa reflect mainly clinical decision making in German centers.

Conclusion

The present survey-based data show that the recommendations of European urologists participating in neoadjuvant, adjuvant, and palliative PeCa case studies on chemotherapy significantly deviate from current EAU guideline recommendations on chemotherapy in PeCa patients. Among several indicators for guideline-adherent therapy decisions, we identified the use of supporting resources (e.g., guidelines, SOPs and medical books) as an essential tool to improve guideline adherence.

Although we did not analyze the reasons for deviations from the EAU guidelines in this first step of E-PROPS, these results once again confirm the noticeable gap between guidelines and implementation in actual clinical practice. Further investigations will have to clarify whether the missing adherence is caused by a low state of individual knowledge of guidelines or rather by the low grade of guidelines recommendations.

Finally, our results encourage the establishment of a European or at least national second-opinion network for PeCa to improve outcomes, equivalent to the German second-opinion network for testicular cancer [20].

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Compliance with ethical standards

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

Ethics statement This study was conducted in accordance with the Declaration of Helsinki in its latest version. This article does not contain any studies with animals performed by any of the authors. Analyzed data were completely anonymized and derived from established databases with rigorous data protection measures. Hence, informed consent was not required.

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