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ORIGINAL ARTICLE

Male Health

Neoadjuvant chemotherapy for patients with locally advanced penile cancer: an updated evidence

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Neoadjuvant chemotherapy (NAC) has shown promising results in patients with locally advanced penile cancer. However, no consensus exists on its applications for locally advanced penile cancer. Thus, it is unclear which kind of chemotherapy regimen is the best choice. Consequently, a systematic search of PubMed, Web of Science, and EMBASE was performed in March 2021 to assess the efficacy and safety of NAC for the treatment of patients with locally advanced penile cancer. The Newcastle–Ottawa Scale was used to assess the risk of bias in each study. This study synthesized 14 published studies. The study revealed that patients who achieved an objective response to NAC obtained a better survival outcome compared with those who did not achieve an objective response. In addition, the objective response rates (ORRs) and pathological complete response (pCR) rates were 0.57 and 0.11, respectively. The incidence of grade ≥3 toxicity was 0.36. Subgroup analysis found that the ORR and pCR of the taxane–platinum (TP) regimen group performed better than those of the nontaxane–platinum (NTP) regimen group (0.57 *vs* 0.54 and 0.14 *vs* 0.07, respectively). Moreover, the TP regimen group had more frequent toxicity than the NTP regimen group (0.41 *vs* 0.26). However, further studies were warranted to confirm the findings.

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Keywords: chemotherapy regimen; locally advanced penile cancer; neoadjuvant chemotherapy; response rate

INTRODUCTION

Penile squamous cell carcinoma (SCC) is a rare disease in Europe with an incidence of 0.9–2.1 per 100 000.[1] SCC accounts for 0.4%–0.5% of malignant tumors in males in developed countries, while the incidence of this disease is 10% in developing countries (*e.g.*, Africa, Asia, and South America).[2,3] Despite its low incidence, the SCC prognosis is poor due to its high rates of metastasis and recurrence.[4]

According to previous studies, partial or total excision of the penis with 3–5 mm width of negative surgical margins is the primary treatment for localized tumor.[5,6] Unfortunately, patients with SCC are usually diagnosed in the advanced stage. At that stage, the lymph node status is important for the prognosis of locally advanced penile cancer.[7] The cancer-specific 5-year survival rates for patients who are lymph node negative (LN^-) and lymph node positive (LN^+) are 71.0% and 33.2%, respectively.[8] The current standard treatment for locally advanced penile cancer is total penectomy or extensive partial amputation with a perineal urethrostomy and regional lymph node dissection.[6,9] Moreover, multimodal treatments were recommended in the guidelines for patients with metastatic SCC, which include preoperative (neoadjuvant) and postoperative (adjuvant) chemotherapy and postoperative (adjuvant) chemoradiotherapy.[10–14]

Neoadjuvant chemotherapy (NAC) is given before surgery to downsize the tumor and mitigate micrometastatic growth. Importantly, previous studies have proved that NAC could shrink the penile tumor and downsize the lymph node metastases, which is meaningful to improve the survival rate in patients with advanced SCC who are LN^- or LN^+.[15–18] However, evidence is limited on its efficacy and safety. Similarly, no consensus exists on the option of the best NAC regimen.[19] The latest European Association of Urology guidelines has recommended using cisplatin- and taxane-based triple combination in patients with SCC who have fixed, unresectable lymph node.[20] However, evidence is weak concerning NAC for locally advanced penile cancer, and further work is necessary.

Several retrospective studies have currently reported the application of NAC for locally advanced penile cancers.[13,15–18,21–29] The efficacy and safety of NAC were assessed to achieve the most up-to-date evidence and explore the optimal chemotherapy regimen.

MATERIALS AND METHODS

Search strategy

The current systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Cochrane Handbook for Systematic Reviews of Interventions.[30] PubMed, Web of Science, and EMBASE were systematically searched in March 2021 to identify relevant studies. The search strategy included terms for "penile cancer" or "neoplasms, penis" or "penis neoplasms" or "cancer of penis" and "chemotherapy" or "neoadjuvant" or "adjuvant." The search was independently performed by PHY and GP.

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Inclusion and exclusion criteria

All database results were imported into an EndNote X7 (EndNote X7, Thomson Reuters, New York, NY, USA) reference manager before screening; then, duplications were removed. Studies that investigated patients who received NAC for treatment of advanced penile cancer were included. In addition, the included patients should be pathologically diagnosed with penile cancer. Letters, reviews, replies from authors, case reports, summaries of meetings, and articles not published in the English language were excluded. Studies with insufficient data were also excluded from the current study. The pieces of literature were independently assessed according to the inclusion criteria by two of the authors (DHC and XNZ).

Outcome

The primary outcomes of this study were objective response rates (ORRs, including complete response [CR] and partial response [PR]) and overall survival rate. Objective tumor response was assessed according to the Response Evaluation Criteria In Solid Tumors (version 1.0 or 1.1).[31,32] Furthermore, 2- and 5-year survival rates were defined as the proportion of patients alive 2 years and 5 years from diagnosis until the last follow-up or mortality from any cause, respectively.

The secondary outcomes of this study were to compare differences in the pathological CR (pCR) rates and overall mortality (OM) between the taxane–platinum (TP) and nontaxane–platinum (NTP) groups.

Data extraction and quality assessment

Two authors (DZL and XYLY) separately conducted literature screening. Baseline characteristics, participant demographics, study period, follow-up time, intervention details, toxicity, and outcomes (defined as the number of responses, 2-year survival rate, 5-year survival, and OM) were extracted for this study. Any disagreements regarding study selection or data extraction were resolved through discussion with a third author. The Newcastle–Ottawa scale (NOS) was adopted to assess the included studies by two participants. Each study with NOS scores of at least 5 was considered a high-quality study.

Synthesis of results and statistical analysis

Statistical analysis was conducted using the RevMan version 5.3.0 (Cochrane Collaboration, Oxford, UK) and R package metafor (Integrated Development for R. RStudio, Inc., Boston, MA, USA). Continuous demographic variables were presented as median, interquartile range, and minimum–maximum range, whereas categorical variables were described by absolute numbers. Risk ratios (RRs) and 95% confidence intervals (95% CIs) were obtained using the Mantel–Haenszel method to evaluate the treatment results. A greater likelihood of survival rate in the responses group is shown when RR >1.0. For all statistical tests, the significance level (α) was set to 0.05, and $P < 0.05$ was considered statistically significant.

Statistical heterogeneity was assessed using the I^2 test ($I^2 < 50\%$) and Chi-square test, while $P < 0.1$ and $I^2 > 50\%$ were identified as heterogeneous. A fixed-effect model would be used if heterogeneity is absent; otherwise, a random-effect model was used. Subsequently, subgroup analysis was conducted for different chemotherapy regimens used in the included studies. In addition, sensitivity analyses were conducted to evaluate the robustness of the meta-analysis results. Publication bias was assessed using funnel plots, Begg's test, and Egger's test. Moreover, $P < 0.05$ indicates a significant statistical risk of publication bias.

RESULTS

Study selection and characteristics

The search conducted in the current study identified 788 articles for review (**Figure 1**), and 584 articles remained for screening after authors removed duplicates. The full text of the remaining articles ($n = 42$) was screened after scrutiny of titles, abstracts, and full-text articles. Consequently, 28 articles were excluded for the following reasons: the unavailability of statistical data in 18 studies, the wrong study design in 8 studies, and the wrong population in two studies. Ultimately, 14 articles met the inclusion criteria.[13,15–18,21–29]

All of the identified articles were retrospective cohort studies (**Table 1**). Of the patients, 382 with locally advanced penile cancer underwent NAC in the current study, with an age range of 24–89 years. Of these, 66 patients received NAC with NTP (including 5-fluorouracil/cisplatin, bleomycin/methotrexate/cisplatin [BMP], and cisplatin/irinotecan), whereas 316 patients were treated with TP (including paclitaxel/ifosfamide/cisplatin [TIP], paclitaxel/carboplatin, and docetaxel/cisplatin/5-fluorouracil). A detailed description of the NAC cycles and follow-up time for each study is shown in **Table 1**. Furthermore, the included studies have a NOS score ≥5, indicating a good level of quality.

Efficacy of NAC

Overall, 14 studies, including 66 NTP and 316 TP group cases, provided the data in terms of ORR. The overall ORRs in the included studies were 0.57 (95% CI: 0.47–0.66), and heterogeneity test showed the result as $I^2 = 65\%$, indicating heterogeneity among studies (**Figure 2**). Subsequently, a subgroup analysis was conducted based on the different chemotherapy regimens. NTP and TP chemotherapy regimens were used in 5 and 10 studies, respectively. Stratification by different chemotherapy regimens demonstrated a significant ORR benefit with TP (ORR = 0.57; 95% CI: 0.46–0.67) compared with NTP (ORR = 0.54; 95% CI: 0.31–0.76).

Concerning pCR rates, the overall rates of the primary articles incorporated in this study were 0.11 (95% CI: 0.05–0.19) with substantial heterogeneity ($I^2 = 55\%$; **Figure 3**). Subgroup analysis found that the pCR rates in the TP and NTP regimen groups were 0.14 and 0.07, respectively.

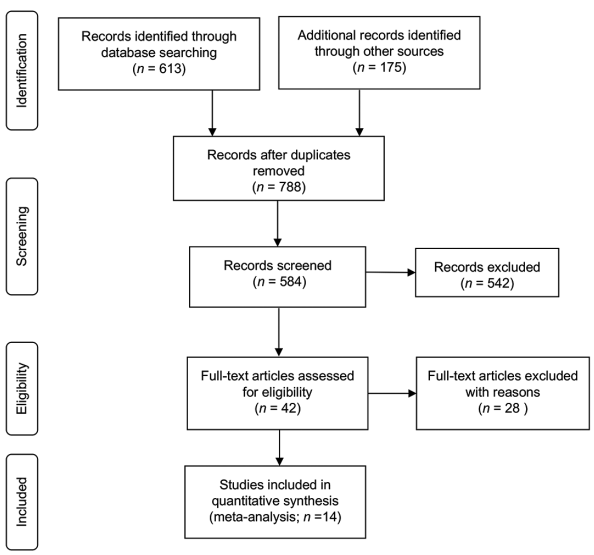

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart.

Table 1: Baseline characteristics of the included studies

Study	*Country*	*Period (year)*	*Chemotherapy regimen*	*Sample size*	*Age (year), median (range)*	*Chemotherapy cycles, median (range)*	*Follow-up (month), median (range)*	*NOS*
Bermejo *et al.*[15] 2007	US	1985–2000	TIP, PC, BMP	10	56 (41–86)	NA	62 (48–84)	7
Theodore *et al.*[29] 2008	The Netherlands	2008–2012	TPF	26	61 (35–73)	NA (2–4)	30 (6–17)	6
Nicholson *et al.*[24] 2013	UK	2009–2010	TPF	29	60.7 (49.7–65.5)	3 (1–3)	14.5 (NA)	7
Pagliaro *et al.*[26] 2010	US	2000–2008	TIP	30	57.5 (24–78)	NA	34 (14–59)	7
Dickstein *et al.*[22] 2016	US	1993–2011	TIP, PC, 5-FU/cisplatin, BMP	60	60.6 (24.5–81.4)	4 (1–10)	53.8 (4.4–160.1)	7
Pizzocaro *et al.*[27] 2009	Italy	2004–2006	Taxanes (T), cisplatin, 5-FU	6	54 (44–74)	2 (2–7)	20.5 (NA)	6
Sitompul *et al.*[28] 2019	Indonesia	2014–2016	TIP	17	44.18±11.13[a]	4 (NA)	7 (1–11)	6
Xu *et al.*[17] 2019	China	2009–2016	TIP	19	56.1 (35–69)	2 (1–2)	39.6 (NA)	6
Theodore *et al.*[29] 2008	Europe	2004–2006	Cisplatin, irinotecan	7	NA	4 (3–4)	NA	5
Chiang *et al.*[21] 2014	China	2005–2013	MTX, mitomycin C, bleomycin, cisplatin, and 5-FU	12	65.5 (33–89)	2 (1–5)	23 (8–72)	6
Leijte *et al.*[13] 2007	The Netherlands	1972–2005	Bleomycin, bleomycin/vincristine/methotrexate, 5-FU/Cis, BMP, cisplatin/irinotecan	20	62 (35–79)	NA	23 (1–134)	6
Zou *et al.*[18] 2014	China	2001–2012	BMP	24	53.4 (38–71)	2 (1–4)	50.1[b] (7–122)	7
Necchi *et al.*[16] 2017	Italy	1990 onward	TPF	94	60.4±10.4[a]	>2	NA	7
Nicolai *et al.*[25] 2016	Italy	2004–2012	TPF (paclitaxel-PF, docetaxel-PF)	28	NA	NA	22 (17–42)[c]	7

[a]Mean±s.d.; [b]mean; [c]median (IQR). TIP: paclitaxel/ifosfamide/cisplatin; BMP: bleomycin/methotrexate/cisplatin; PC: paclitaxel/carboplatin; TPF: docetaxel/cisplatin/5-fluorouracil; MTX: methotrexate; 5-FU: 5-fluorouracil; NOS: the Newcastle–Ottawa scale; NA: not available; s.d.: standard deviation; IQR: interquartile range

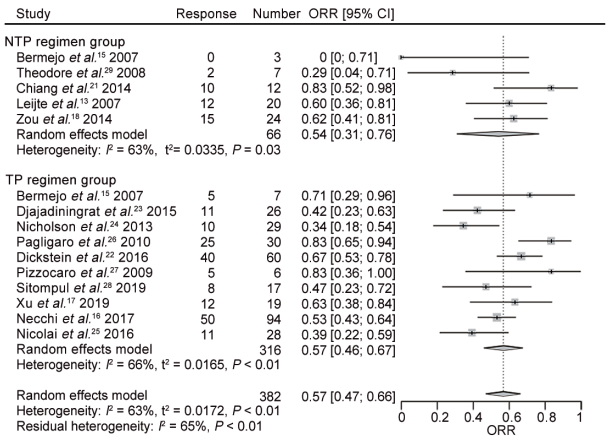

Figure 2: Forest plot of objective response rates for patients with advanced penile cancer followed by neoadjuvant chemotherapy. TP: taxane–platinum; NTP: nontaxane–platinum; ORR: objective response rate; CI: confidence interval.

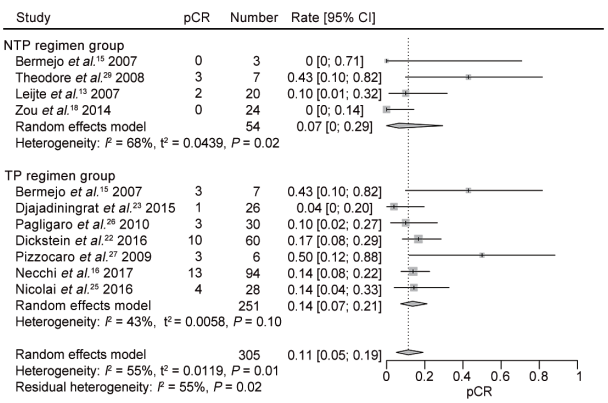

Figure 3: Forest plot of pathological complete response rates for patients with advanced penile cancer followed by neoadjuvant chemotherapy. TP: taxane–platinum; NTP: nontaxane–platinum; pCR: pathological complete response; CI: confidence interval.

Moreover, the 2- and 5-year survival rates between the responder (CR and PR) and nonresponder (SD and PD) groups were compared. The pooled analysis of 4 of 14 studies that included 124 patients showed that patients who responded to NAC had significantly better 2-year survival rates compared with those who did not respond to NAC with RRs of 4.67 (95% CI: 1.45–15.02; $P = 0.01$; **Figure 4a**). Similarly, the 5-year overall survival rates revealed comparable results with RRs of 4.09 (95% CI: 1.90–8.82; $P = 0.0003$; **Figure 4b**).

Safety of NAC

Of all included studies, 11 reported toxicity. **Supplementary Table 1** shows that hematologic toxicity was the most common toxicity reported during all phases. Moreover, nonhematological toxicity, including digestive toxicity, cardiovascular toxicity, and alopecia, was also not infrequent after NAC. Moreover, grade ≥3 toxicity was observed in 84 patients, and the incidence of toxicity was 0.36 (95% CI: 0.18–0.57) with substantial heterogeneity ($I^2 = 86\%$; **Figure 5**). Subgroup analysis found that the incidence of grade ≥3 toxicity in the TP and NTP regimen groups was 0.41 and 0.26, respectively.

Ten studies (229 cases) reporting OM rates were analyzed. The OM was 0.61 (95% CI: 0.55–0.68) with substantial heterogeneity ($I^2 = 45\%$; **Supplementary Figure 1**). A subgroup analysis found that the OM in the TP and NTP regimen groups was 0.64 and 0.46, respectively.

Publication bias and sensitivity analysis

Supplementary Figure 2 shows the results without evidence of publication bias, which was assessed by funnel plots. In addition, the results of Egger's test (ORR: $P = 0.7958$, pCRs: $P = 0.9956$, toxicity rates: $P = 0.2332$, and OM: $P = 0.5178$) suggested that no significant publication bias was observed in the included studies. Sensitivity analysis indicated that removal of any study from the analysis did not alter the result of the present pooled analysis (data not shown).

DISCUSSION

The current study demonstrated that patients who responded to NAC had significantly better 2- and 5-year survival rates compared

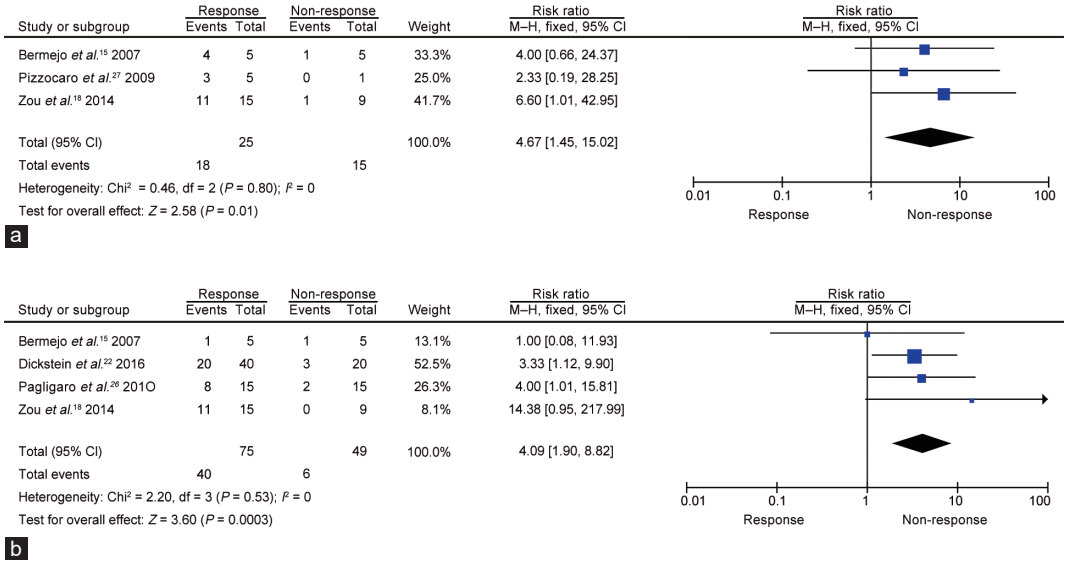

Figure 4: Forest plot of the (**a**) 2-year and (**b**) 5-year survival rates for the responder versus nonresponder group. M–H: Mantel–Haenzel; CI: confidence interval; df: degree of freedom.

with those who did not respond. The ORRs and pCR rates were 0.57 and 0.11, respectively. Moreover, among mentioned two outcomes performed better in patients treated with the TP regimen. In terms of treatment safety, the incidence of toxicity and OM were 0.36 and 0.61 in the TP and NTP regimen groups, respectively.

Surgery alone cannot achieve the goal of disease-free and long-term survival for patients with regionally advanced SCC.[26] Patients who have pelvic or inguinal lymph node metastases should be treated with comprehensive treatment. Radiotherapy has shown favorable results in organ preservation and the survival rates for early-stage SCC,[33,34] and it may be considered for patients with advanced metastasis and who are unable to receive surgery.[35] Nevertheless, insufficient evidence exists to validate its effectiveness. In addition, radiotherapy not only leads to a relatively high incidence of side effects but also tends to lead to edema of the lymph nodes.[36] Adjuvant chemotherapy has been an increasingly used treatment approach, and several studies have demonstrated that patients could obtain a favorable objective reaction.[10,37,38] However, disease progression was found in the majority of patients, and no statistical difference was noted in the survival analysis.[39] Meanwhile, patients are frail after surgery and have difficulties in tolerating the chemotherapy, which is a major shortcoming involving drug resistance and toxicological side effects. Therefore, the application of NAC for advanced penile cancer is focused.

NAC has been used in penile cancer treatment since the late 1980s and is a promising SCC treatment.[40,41] In addition, NAC can both effectively shrink the tumor mass and reduce inguinal lymph node metastasis, thus achieving a therapeutic effect. Previous studies demonstrated that NAC significantly improves overall survival in patients with advanced LN^+ penile cancer compared with surgery alone.[42] In the current study, the ORR after NAC was found to be 0.57 (95% CI: 0.47–0.66), and all studies except for three[24,25,29] achieved relatively high ORR. Furthermore, the pCR rate ranged from 0 to 0.43. Pizzocaro *et al.*[27] and Theodore *et al.*[29] reported a higher pCR rate (50% and 43%, respectively), while other studies demonstrated a lower rate. This may be due to the small number of patients in these studies.[16,22] The largest number of patients among all included studies reported similar pCR, which was about 15%. Notably, the 5-year survival rates in patients who respond to NAC were significantly higher than those who did not respond, and a similar result was found in the 2-year survival rates. Patients who achieved a stable disease following NAC have a better OS after surgery compared with those who have progressive disease (median OS of 41 months and 11 months, respectively).[22] Therefore, the patients' response to NAC may be an independent prognostic marker for locally advanced SCC, and patients with a good response to NAC are more likely to benefit from surgery, which helps guide treatment decisions.

Different NAC may have variable ORRs and toxicity. The most commonly used chemotherapy agents are bleomycin, methotrexate, cisplatin, 5-fluorouracil, paclitaxel, and ifosfamide. Dexeus *et al.*[38] demonstrated that 14 patients with advanced penile cancer obtained a 72% response rate following combination treatment with cisplatin, methotrexate, and bleomycin. A retrospective study included 13 patients, of which 9 patients achieved response after receiving NAC with cisplatin and interferon-α2B. In addition, eight patients remained disease-free for 21 months.[43] In a review, Culkin and Beer[19] reported that 35 patients who administered cisplatin-based NAC had a clinical response rate of 69%. However, thus far, no standard NAC regimens, doses, and cycles have been established for advanced penile cancer, despite TIP being the most accepted regimen for NAC. In the current study, NAC regimens were classified into two broad categories: NTP and TP. By conducting stratified analyses, TP regimens were found to show comparable ORR and OM, and the pCR rate was higher in patients treated with TP regimens (0.14 *vs* 0.07). However, the difference did not reach statistical significance. Notably, the incidence of toxicity is more frequent in the TP regimen than that in the NTP regimen (0.41 *vs* 0.26). Among the included studies, the number of patients treated with the TP regimen is significantly larger than that with the NTP regimen.

Zou *et al.*[18] accounts for majority of the NTP group that included 24 patients with locally advanced penile cancer receiving NAC with a BMP. The pCR rate was 0, which may be explained by the patients' stage N3 inguinal node. Moreover, the dose of chemotherapeutic agents in this study was relatively low and may result in a toxicity rate of 4%. Theodore *et al.*[29] reported a pCR rate of 43% after a median of four

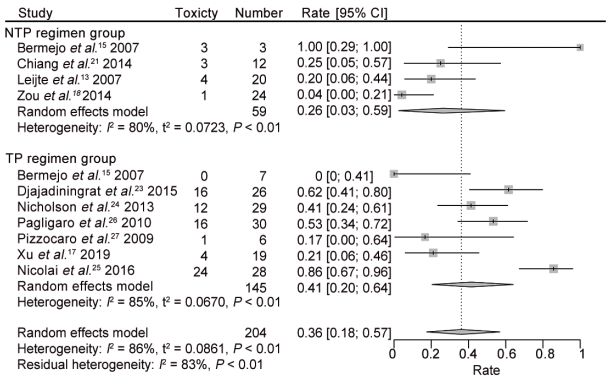

Figure 5: Forest plot of the incidence of toxicity for patients with advanced penile cancer followed by neoadjuvant chemotherapy. TP: taxane–platinum; NTP: nontaxane–platinum; CI: confidence interval.

NAC cycles, while other studies in the NTP group only intervened in a median of two NAC cycles. In addition, this study did not report the lymph node stage of the patients, and most of the patients in the NTP group were diagnosed with stage N3 inguinal node.[13,15,18] Necchi *et al.*[16] reported that patients had completed two or more chemotherapy cycles, and the ORR and pCR rate were 53% and 14%, respectively. However, the toxicity had not been assessed. Furthermore, the ORR and pCR rate were comparable in several studies that used TP for NAC.[16,23,25,28]

Undoubtedly, toxicity is associated with the administration method of chemotherapeutic drugs (including regimens, dose, and cycles) and conditions of individuals. Looking across the results, toxicity was more frequently observed in patients treated with paclitaxel than that in the docetaxel group. This finding is consistent with a previous study.[44] Moreover, high regimens had more severe and more frequent toxic reactions than low regimens.[18,25] Of note, all patients treated with BMP suffered severe toxicity in the study of Bermejo *et al.*[15]

Although one systematic review has been published on the efficacy of NAC for locally advanced penile cancer,[45] some differences exist between that study and the current study. First, a comprehensive search of databases was conducted to ensure that all relevant articles were identified. Thus, the current study included 14 studies, while they only had 10. Second, ORRs, pCR rates, 2- and 5-year survival rates, and OM were selected as potential outcomes; thereby, the efficacy of NAC could be evaluated more comprehensively in the present study than that in their study. The current study revealed that patients who achieved an objective response to NAC obtained a better survival outcome compared with those who did not achieve an objective response. This means that patient response to NAC may be an independent prognostic marker for locally advanced SCC. These findings are not represented in their study. However, the current study has some limitations. First, all of the identified studies were retrospectively designed, and all of the included trials were single-arm designed. Second, 382 patients were included, the sample size was small, and few studies did not report chemotherapy cycles. Third, the study population is heterogeneous, which was probably derived from differential lymph node staging and the cycle, dose, and type of chemotherapy drugs. Finally, the efficacy of NTP- and TP-based NAC regimens was not compared, and the specific regimens need to be further explored. Therefore, additional larger-scale randomized studies are needed to confirm the findings of the present study.

CONCLUSION

In conclusion, the current study demonstrated that the 2- and 5-year survival rates significantly improved among patients who achieved an objective response to NAC compared with those who did not. Importantly, patient response to NAC may be an independent prognostic marker for locally advanced SCC. Furthermore, the overall response rate of patients to NAC was 0.57 and the pCR was 0.11. Subgroup analysis found that the ORR and pCR rate of the TP regimen group were better than those of the NTP regimen group (0.57 *vs* 0.54 and 0.14 *vs* 0.07, respectively). However, the TP regimen group had more frequent toxic reactions than the NTP regimen group (0.41 *vs* 0.26). Thus, using NAC in patients with locally advanced penile cancer is more meaningful. However, randomized and high-quality studies are warranted to confirm the results of this study.

AUTHOR CONTRIBUTIONS

JZA and LY conceived the project, XYLY and DHC drafted the manuscript, PHY, XYX and GP searched the databases, DHC, XNZ, and DZL analyzed data, and HL and JZA revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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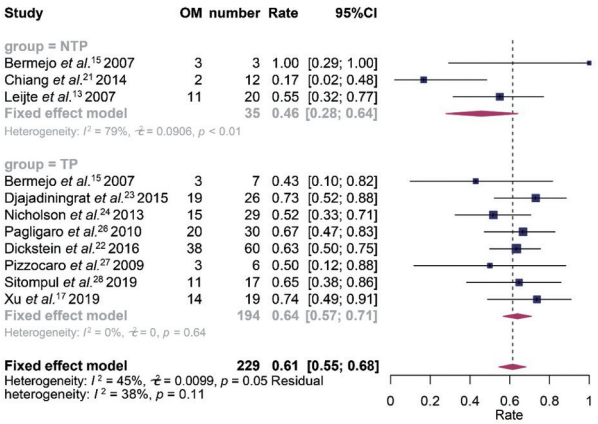
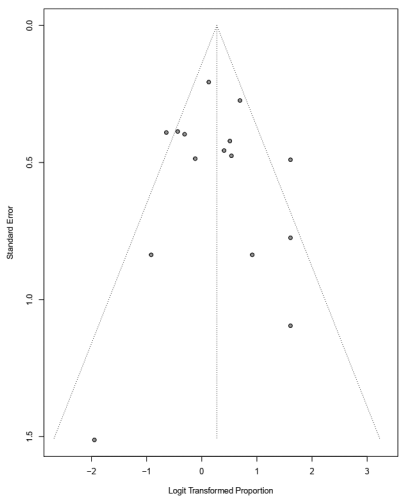


Supplementary Figure 1: Forest plot of the overall mortality for patients with advanced penile cancer followed by neoadjuvant chemotherapy. TP: taxane–platinum; NTP: nontaxane–platinum; OM: overall mortality.



Supplementary Figure 2: Funnel plot for the included studies.

Supplementary Table 1: Summary of adverse events

Event	*Grade 1*	*Grade 2*	*Grade 3/4*
Digestive system			
Anorexia	2	5	
Diarrhea		2	9
Nausea/vomiting	10	23	8
Oral mucous damage	4	9	8
Hematological system			
Anemia		2	23
Febrile neutropenia			8
Neutropenia			35
Leucopenia			4
Hypocalcemia		4	
Hypokalemia		4	1
Hypomagnesemia		2	6
Thrombocytopenia			9
Central nervous system			
Fatigue	1	7	2
Dysgeusia		4	
Syncope			5
Motor neuropathy	1	1	1
Cardiovascular system			
Acute coronary syndrome		2	
Atrial fibrillation		1	
Chest pain		1	
Myocardial ischemia	1	1	2
Heart failure			1
Urinary system			
Acute renal failure	1		
Acute kidney injury		2	2
Infection			
Abdominal infection			1
Pneumonia			1
Sepsis			7
Toxicity			26
Bone marrow suppression	16	17	4
Deep venous thrombosis			2
Peripheral edema		2	2
Allergic reaction		4	1
Alopecia			25