Comparison of Early Inguinal Lymph Node Dissection and Neoadjuvant Chemotherapy in Penile Cancer Patient with Bulky Nodal Metastasis: A Cohort Study

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ABSTRACT

Introduction

Penile cancer is a rare malignancy, where extranodal extension in inguinal or pelvic lymph nodes is associated with decreased 5-year cancer-survival rate in this study, we try to assess survival and quality of life in a penile cancer patient with bulky lymph node.

Method

We retrospectively reviewed data from penile cancer patients with bulky lymph nodes who underwent treatment between July 2016 and July 2021 at tertiary referral hospital care. The inclusion criteria (age >18 yr, histologically proven penile cancer, and completion of last treatment 6 months prior to this study) yielded a cohort of 20 eligible penile cancer patients with bulky lymph nodes (> 4 cm/bilateral mobile/unilateral fixed). Only patients who had completed therapy at least 6 months prior to the study were included. After obtaining consent, they were asked to complete the EORTC QLQ-C30 questionnaire to evaluate the patient quality of life.

Results

Out of 20 patients, 5 patients underwent direct ILND and 15 patients underwent chemotherapy. Median follow-up after primary diagnosis was 114±32 months in patient with early ILND and 52±11 months in patients who underwent delayed lymph node dissection. Out of 5 patients underwent early ILND, all of them survived during follow-up, and achieve cancer-free status without residual tumor and with excellent functional outcome (Karnofsky 90). There is no significant difference in social function (p value = 0.551), physical function (p value = 0.272), role function (p value = 0.546), emotional function (p value = 0.551), cognitive function (p value = 0.453), and global health status (p value = 0.893) between patient which treated with early ILND and Neoadjuvant Chemotherapy. However, patient who underwent early ILND showed a relatively better clinical outcome.

Conclusion

Early ILND followed by adjuvant chemotherapy for penile cancer with palpable lymph nodes is more favourable than neoadjuvant TIP chemotherapy.

Keywords: Penile cancer, lymph node, dissection, neoadjuvant chemotherapy, bulky nodal

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Introduction

Penile cancer is a rare malignancy in less than 1% of all malignancies in the United States and European countries. However, the incidence is higher in developing countries, with rates of 2.8–6.8 per 100 000. This high rate is associated with circumcision in developing countries. Male neonatal circumcision is associated with A low incidence of penile cancer in countries such as Israel, where the penile cancer rate is less than 0.1 %. Other risk factors are phimosis, obesity, lichen sclerosis, chronic inflammation, smoking, UVA phototherapy, low socioeconomic status, human papillomavirus (HPV) infection, and immune-compromised states.[(1)]

In the early stages, penile cancer is highly treatable. Social stigma, fear, and embarrassment often make patients reluctant to seek treatment and become delayed. The Glans penis is the most common site for penile cancer, followed by the prepuce, glans, coronal sulcus, and shaft (uncommon). Squamous cell carcinoma accounts for 95% of diagnosed lesions and is the most common histologic subtype. [(1)]

TIP is a chemotherapy treatment named after the initials of the used chemotherapy drugs: paclitaxel (**T**axol), **I**fosfamide, and cisplatin (**P**latinum).[(2)] Based on the current NCCN Penile Cancer guideline 2021, neoadjuvant chemotherapy is given in the treatment of penile cancer with bulky lymph nodes/bilateral mobile/unilateral fixed Follwed by Bilateral ILND if patient Has Complete/Partial Response Disease after NAC. After being given TIP chemotherapy, the lymph node will be evaluated, and then, if complete or partial response were found, then lymph node dissection is indicated. However, this approach carries a risk of lymph nodes being unresectable if waiting longer to conduct lymph node dissection or Became progressive disease. Penile cancer 5-year survival rate in patients with palpable lymph nodes ranges between 5-30%, depending on metastasis status and lymph node numbers.[(3)]

Pathologic TNM staging is post-surgery prognostic stratification, and extranodal extension in inguinal or pelvic lymph nodes is associated with decreased 5-year cancer-survival rate (42% ad 22%, respectively). Nomograms have been reported to predict cancer-specific survival and LN metastasis for patients following penectomy. These nomograms consist of multiple variables in addition to the stage. Adding multiple variables enhances prognostication, including grade, venous or emboly in the lymphatic system, and surgery type. Other studies also reported lymph node density, lack of koilocytosis, and clear cell subtype as prognostic factors.[(4)]

In addition, molecular prognostic markers are suggested in some studies, such as p53, Ki-67, E-cadherin, MMP-9 (matrix metalloproteinase-9), annexins I and IV, and decreased KAI1/CD82. Although HPV is associated with high-grade tumours, the impact on outcomes reamins unclear from one study to another study.[4] Even though numerous studies focus on survivability in penile cancer patients, there is still not yet adequate research covering the relationship between early bilateral ILND compare to NAC TIP before ILND in Bilateral Mobile lymph nodes metastasis. To date, only one research focuses on the relationship between aggressiveness in surgery and quality of life in penile cancer patients. In this study, we try to assess survival and quality of life in a penile cancer with bilateral lymph nodes metastasis compare to neoadjuvant chemotherapy TIP 4 cycle as it suggested by NCCN Penile Cancer Guideline 2021.

Method

After obtaining institutional review board approval, we retrospectively reviewed data from penile cancer patients with bulky lymph nodes who underwent treatment between July 2016 and January 2022 at tertiary referral hospital care. The inclusion criteria (age >18 yr, histologically proven penile cancer, and completion of last treatment 6 months prior to this study) yielded a cohort of 20 eligible penile cancer patients with bulky lymph nodes (> 4 cm/bilateral mobile/unilateral fixed lymph nodes metastasis). All patients were contacted by mail or phone or during clinic visits. After obtaining consent, they were underwent clinical examination and asked to complete the EORTC QLQ-C30 questionnaire to evaluate the patient quality of life; it is a validated oncology-specific survey that evaluates global health status (GHS), cognitive, social, physical, emotional, and role functioning. The EORTC QLQ-C30 also assesses physical symptoms such as fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance, financial burden, and treatment-specific side effects such as ototoxicity and peripheral neuropathy. A high score for a functional scale represents a healthier level of functioning, while a high score for a symptom scale represents increased severity of symptoms.

Result

Median follow-up after primary diagnosis was 24.5±6.7 months in patient with early ILND and 36.8±9.4 months in patients who underwent NAC (TIP 4 cycle) followed by lymph node dissection. Out of 20 patients, 5 patients underwent direct ILND and 15 patients underwent chemotherapy. In early ILND group follow-up was conducted since ILND surgery, while in chemotherapy group follow-up was conducted after 4 cycle of TIP chemotherapy was done. The clinical and histological characteristics of the 2 treatment groups are shown in table 1. Patient and primary tumor characteristics were distributed similarly between both groups. Prior to intervention, patients on both groups were in excellent condition (Karnofsky score: 90).

Disease Progression and Survival

As shown in the figure, the disease specific survival rate and progression was significantly better in patients with early ILND. Out of 5 patients underwent early ILND, all of them survived during follow-up, and achieve cancer-free status without residual tumor and with excellent functional outcome (Karnofsky 90). Out of 15 patients that underwent chemotherapy, only 5 are eligible to underwent ILND. Among those four, only one of them. While the rest are

having poorer outcome, according to RECIST criteria patients's disease are progressing. Mortality rate is 20% in patient who underwent neoadjuvant chemotherapy after bulky lymph node diagnosis, while three others are lost to follow-up.

Quality of Life Result

There is no significant difference in social function (p value = 0.551), physical function (p value = 0.272), role function (p value = 0.546), emotional function (p value = 0.551), cognitive function (p value = 0.453), and global health status (p value = 0.893) between patient which treated with early ILND and Neoadjuvant Chemotherapy. The mean values for subscales of QLQ C-30 questionnaire can be seen in figure 1.

However, patient who underwent early ILND showed a relatively better clinical outcome. All of those five has an unchanged Karnofsky score compared to the prior intervention. In the other hand, patients who received chemotherapy which followed by ILND has a relatively lower body mass index, lower Karnofsky score, and poorer nutritional status.

Discussion

Survival Analysis and Quality of Life

A phase II trial by Pagliaro et.al[6] shows 17.1 months of overall survival. Of 30 penile cancer patients in this trial, 15 (50.0%) had an objective response, and 22 (73.3%) underwent surgery. Three (10%) patients had pathologic complete response (pCR), a substantial predictor of improved survival.

Remember that the primary endpoints studies are progression-free survival (PFS) and overall survival (OS). PFS is a period from the beginning of chemotherapy until clinically or radiologically documented disease progression or death from any causes. OS is the period from the start of chemotherapy to patient death of any cause. PFS and OS were calculated with Kaplan–Meier survival curves. The Kaplan-Meier survival curve is not available in the article.

In conclusion, ITP chemotherapy was effective in terms of conventional response rate and overall survival in 10% of patients.[6]

Regarding the quality of life, patients were asked to complete EQ5D questionnaires before the first, third, and fifth chemotherapy cycle and between 4 and 6 weeks after the last chemotherapy cycle at the end of treatment (EOT). Only three patients completed the questionnaires at multiple time points. There was no difference in the scoring, whether in individual domains or in the global health score in these three patients at various time points.[6]

Another study involved 19 patients with advanced penile cancer receiving neoadjuvant chemotherapy of ITP regimen from June 2009 to June 2016 in China. After a median follow-up of 39.6 months, 11 of 19 patients have progressed, and 14 patients died, with an estimated median PFS of 11 months (95% CI, 6.734 to 15.266) and OS of 23 months (95% CI, 6.122 to 39.898).[7]

This study shows statistically significant improvement in PFS and OS among patients who experienced objective response to neoadjuvant chemotherapy (group A) compared with did not respond to chemotherapy (group B) (log-rank test; $P<0.001$).[7]

Even though several studies below showed that neoadjuvant chemotherapy was effective and recommended for penile cancer with bulky lymph nodes, we found a new fact that it would be beneficial for the patient to receive early ILND instead of neoadjuvant TIP Chemotherapy. The reason is are there is a risk that the cancer is chemo-resistant, which later progresses rapidly and becomes unresectable. As mentioned above, this study illustrates that the four patients who received early ILND instead of TIP chemotherapy have a similar quality of life and longer lifespan. This study could be the basis for reconsidering direct ILND resection when compared with doing neoadjuvant chemotherapy first as directed by NCCN guideline, which could lead to unresectable inguinal lymph nodes if physicians delay resection to do chemotherapy first. In our study 25% of patient whose disease progressed, have a poor prognosis and not responding even to second line chemotherapeutic agent with radiotherapy. This finding is supported by several literatures and studies. In a study conducted by Galbiati et al., cutaneous squamous cell cancer is showed as a relatively chemo-resistant.[8] Similar finding also presented in research conducted by Gruhl et al in 2019. They found that non-metastatic pancreas SCC histopathology showed poor response to chemotherapy.[9] This characteristic is likely linked to SCC histopathology. A study which focuses on comparison between SCC type Cervical Cancer and Non-SCC Cervical Cancer also provided similar result. SCC type Cervical Cancer has a significantly higher percentage to become progressive disease (68%) compared to their Non SCC counterparts.[10]

There are several limitations to this study. It is retrospective in nature with relatively small sample size. The QLQ questionnaire is a single questionnaire at a single time point rather than a serial assessment monitoring the change in the patient's QoL over time. Finally, although all patients had completed treatment at least 6 months prior to enrolment, there was no standardized method regarding the specific duration from therapy completion. Despite these shortcomings, this study is one of the first to explore the impact of early ILND in terms of overall QOL outcome and survival in penile cancer with bulky lymph node.

Conclusion

In the NCCN penile cancer guideline 2021, TIP chemotherapy is one of the treatments of choice for Penile Cancer with bulky lymph nodes as neoadjuvant chemotherapy prior to ILND. However, we found a contradictory result during our observation. Out of 20 patients, five who underwent ILND without TIP chemotherapy survived and had a similar or even better quality of life and lower mortality percentage compared to their counterparts. Therefore, according to our clinical observation and finding, early ILND followed by adjuvant chemotherapy for penile cancer with palpable lymph nodes is more favourable than neoadjuvant TIP chemotherapy.

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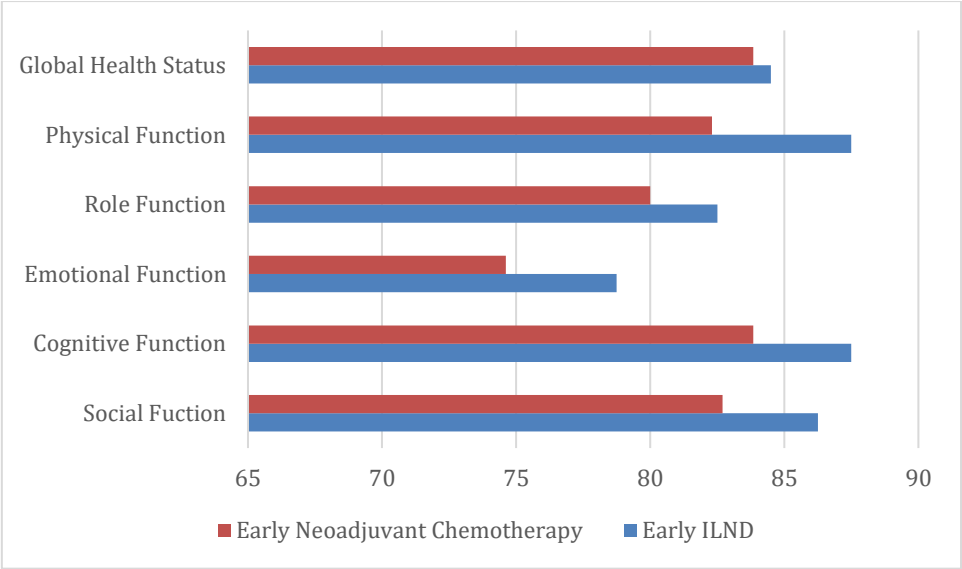

Figure 1. Mean values for sub-scales of the QLQ C-30 questionnaire

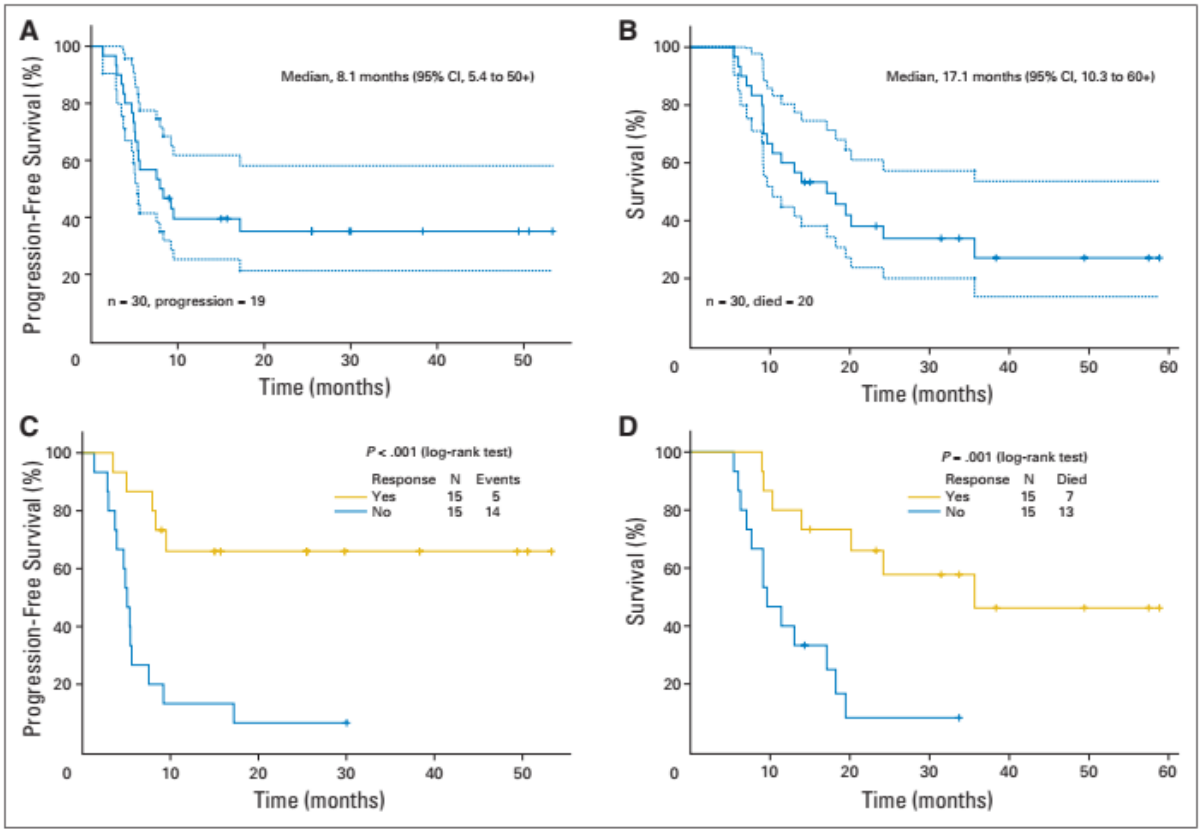

Figure 2. Kaplan-Meier plots (with 95% CIs as dotted lines) of (A) time to progression of the disease and (B) overall survival; patients are grouped by the response for (C) time to progression and (D) overall survival.

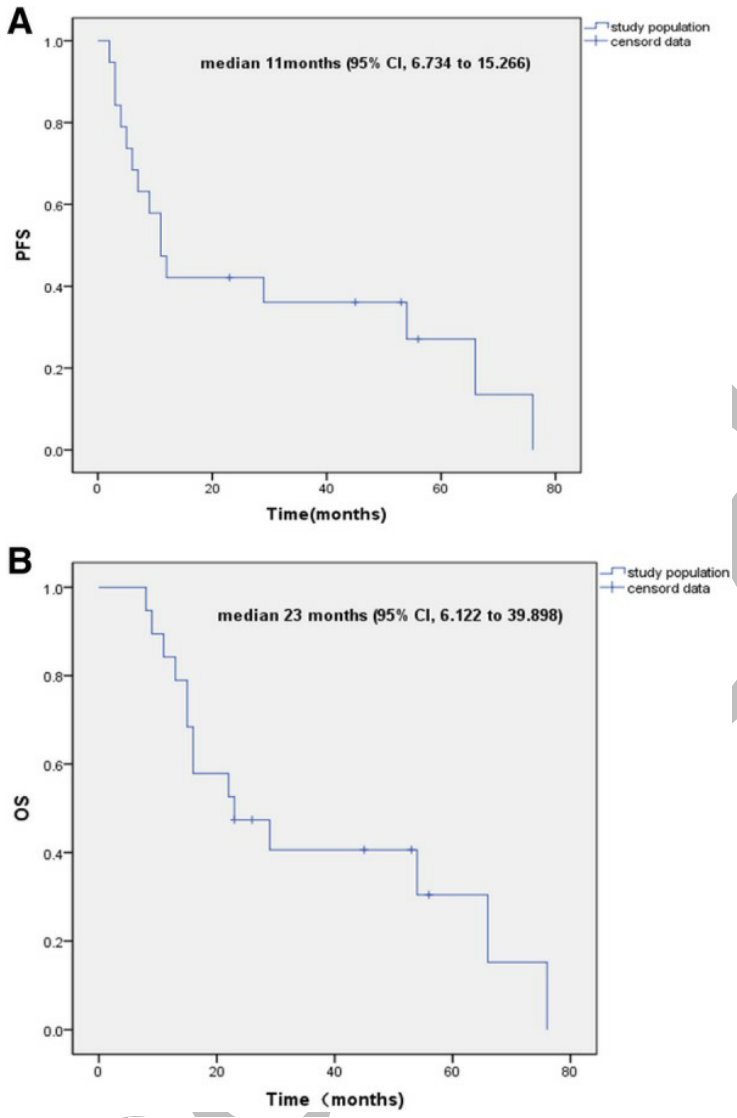

Figure 3. Kaplan-Meier curves show PFS and OS in all patients[6]

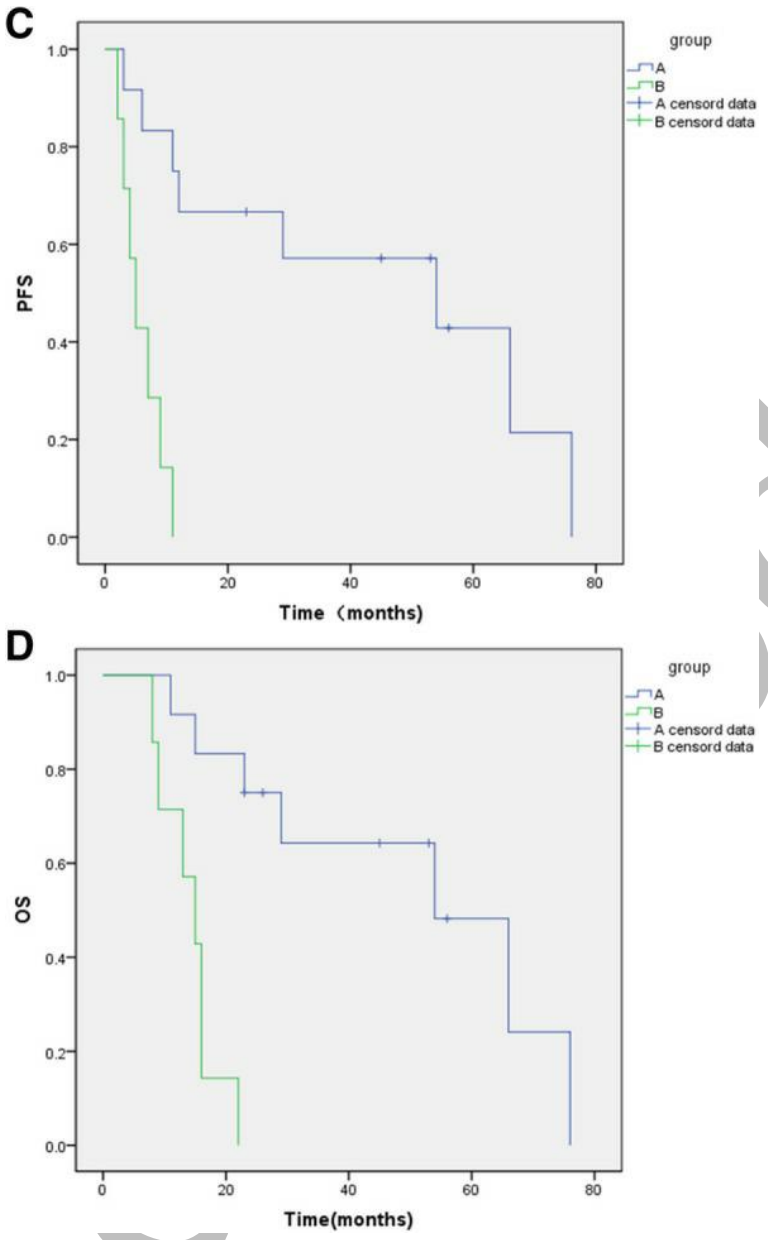

Figure 4. Kaplan-Meier curves show PFS and OS in patients who experienced an objective response (group A) to neoadjuvant chemotherapy compared with those among patients who did not (group B)

Table 1. Study sample characteristics

	Early Resection	**Neoadjuvant chemotherapy**	**P value**
No. of Subject	5	15	
Mean Age	42.4±2.1	44.2±1.8	0.62
No. of death	0	3	0.003

Clinical T Stage			
T2	1	5	0.67
T3	4	10	0.38
Pathological T Stage			
T2	2	5	0.12
T3	3	10	0.14
Tumor Stage			
IIIB	3	11	0.16
IV	2	4	0.36
Vascular invasion			
Absent	1	4	0.34
Present	4	11	0.51

Table 2. Comparison of Karnofsky score between early ILND and NAC + ILND

	Early ILND	**NAC + ILND**	**P value**
No. of Subject	5	4	
Karnofsky Score			
90	5	1	
80		1	
70		2	
BMI	22.3±0.5	18.2±1.8	0.048

Table 3. Study About Chemotherapy with ITP As The Sole Regimen[3]

Author	Regimen	Design	N	Surgery N (%)	Clinical Stage	Clinical Response	Pathologic Complete Response N (1%)	Median Progression-Free Survival	Median Overall Survival
Pagliaro et al.[5]	ITP	Phase II trial	30	22 (73.3)	Any T, N2–N3	15 (50)	3 (10)	8.1 months	17.1 months