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Management of penile cancer in a Singapore tertiary hospital

Teck Wei Tan *, **Sing Joo Chia**, **Kian Tai Chong**

Tan Tock Seng Hospital, Singapore, Singapore

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KEYWORDS

Inflammatory markers;
Inguinal;
Lymph node;
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Penis

ABBREVIATIONS

BMI, body mass index;
CIS, carcinoma *in situ*;
CRP, C-reactive protein;
CSS, cancer-specific survival;
DSNB, dynamic sentinel node biopsy;
EAU, European Association of Urology;
HPV, human papillomavirus;

Abstract ***Objectives:*** To present our experience of managing penile squamous cell carcinoma (SCC) in a tertiary hospital in Singapore and to evaluate the prognostic value of the inflammatory markers neutrophil–lymphocyte ratio (NLR) and lymphocyte–monocyte ratio (LMR).

Patients and methods: We reviewed our prospectively maintained Institutional Review Board-approved urological cancer database to identify men treated for penile SCC at our centre between January 2007 and December 2015. For all the patients identified, we collected epidemiological and clinical data.

Results: In all, 39 patients were identified who were treated for penile SCC in our centre. The median [interquartile range (IQR)] follow-up was 34 (16.5–66) months. Although very few (23%) of our patients with high-risk clinical node-negative underwent prophylactic inguinal lymph node dissection (ILND), they still had excellent 5-year recurrence-free survival (RFS; 90%) and cancer-specific survival (CSS; 90%). At multivariate analysis, higher N stage was significantly associated with worse RFS and CSS. Patients with a high NLR ($\geq$2.8) had significantly higher T-stage ($P = 0.006$) and worse CSS ($P < 0.001$) than those with a low NLR. Patients with a low LMR (<3.3) had significantly higher T-stage ($P = 0.013$) and worse RFS ($P = 0.009$) and CSS ($P < 0.022$) than those with a high LMR.

Conclusions: Although very few of our patients with intermediate- and high-risk clinical node-negative SCC underwent prophylactic ILND, they still had excellent 5-year RFS and CSS. However, survival was poor in patients with node-positive

* Corresponding author at: 11 Jalan Tan Tock Seng, Singapore 308433, Singapore.
E-mail address: teck_wei_tan@ttsh.com.sg (T.W. Tan).

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ILND, inguinal lymph node dissection;
IQR, interquartile range;
LMR, lymphocyte–monocyte ratio;
NCCN, National Comprehensive Cancer Network;
NLR, neutrophil–lymphocyte ratio;
RFS, recurrence-free survival;
SCC, squamous cell carcinoma

disease. The pre-treatment NLR and LMR could serve as biomarkers to predict the prognosis of patients with penile cancer.

Introduction

Penile squamous cell carcinoma (SCC) is uncommon in developed nations, including Singapore. In Singapore, the age-standardised incidence rate for penile cancer between 2003 and 2007 was 0.94 per 100,000 person years [1]. This means that penile cancer only accounted for ~0.4% of all cancers in males in Singapore. Despite the low incidence, penile cancer is often aggressive and treatment usually results in significant morbidity, including its impact on the psychology and sexuality of patients. Risk factors for the development of penile SCC include phimosis, tobacco use, balanitis, chronic inflammation, and human papillomavirus (HPV) infection [2].

In addition to the management of the primary penile SCC, both the National Comprehensive Cancer Network (NCCN) [3] and the European Association of Urology (EAU) [4] clinical practice guidelines emphasise that the management of the regional lymph nodes is decisive for long-term survival of the patient. Both guidelines subdivide patients with clinically normal lymph nodes (cN0) into low-risk (Tis, Ta and pT1a), intermediate-risk (pT1b, Grade 1 or 2) or high-risk (pT1b, Grade 3 or 4; any pT2 or greater) groups. Patients with low-risk SCC can be managed by surveillance, but both guidelines recommend invasive nodal staging with either bilateral modified inguinal lymph node dissection (ILND) or dynamic sentinel node biopsy (DSNB) in patients with intermediate- or high-risk disease. The reason for this recommendation is that early ILND in patients with clinically node-negative penile SCC results in far superior long-term survival compared to therapeutic lymphadenectomy when regional nodal recurrence has occurred [5].

However, ILND is associated with high rates of post-operative complications [6]. In patients with clinically negative inguinal lymph nodes but considered at intermediate-risk, only up to 30% of them will harbour micro-metastatic disease after ILND. This means that up to 70% of these patients will go through ILND with no clinical benefit. To better select patients for ILND, various groups have investigated the prognostic role of biomarkers. Biomarkers purported to be associated with lymph node metastasis include: tissue markers, e.g. over-expression of p53 and Ki-67, and loss of membranous E-cadherin in biopsy or penectomy tissue specimens. However, these tissue markers are of limited use in clinical practice as the standard threshold of positivity is not well defined [7].

Due to the link between cancer development and systemic inflammation [8], more recent reports have evaluated the prognostic role of serum inflammatory markers. Elevated C-reactive protein (CRP) has been reported to be associated with nodal metastasis and poorer cancer-specific survival (CSS) [9,10], and a high neutrophil–lymphocyte ratio (NLR) has also been shown to predict poor CSS in patients with penile cancer [11]. Another potential biomarker, the absolute lymphocyte count–absolute monocyte count ratio (LMR) has been shown to be able to predict clinical outcomes of patients with cancer, including colorectal cancer, sarcoma and lymphoid neoplasms [12–14]. However, there has been no study evaluating its role in providing prognostic information in patients with penile cancer.

In the present study, we present our experience of managing penile squamous cell carcinoma (SCC) in a tertiary hospital in Singapore and evaluate the prognostic value of the inflammatory markers NLR and lymphocyte–monocyte ratio (LMR).

Patients and methods

We reviewed our prospectively maintained Institutional Review Board-approved urological cancer database to identify men treated for penile SCC at our centre between January 2007 and December 2015. Epidemiological and clinical data, including age, smoking history, circumcision status, body mass index (BMI), preoperative full blood count results, TNM staging, tumour