Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Early Inguinal Lymphadenectomy is Necessary in the Treatment of Penile Cancer T1G2.

Jing li (lijingzlyy@163.com)
Guangzhou Medical University Affiliated Cancer Hospital https://orcid.org/0000-0003-3145-0963
Zai-shang Li
Shenzhen People's Hospital
Bin Wang
Guangzhou Medical University Affiliated Cancer Hospital
Jian-an Yang
Guangzhou medical university affliated cancer hospital

Research article

Keywords: penile cancer, squamous cell carcinoma, lymphadenectomy, survival

Posted Date: May 19th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27609/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Backgroud：At present, there is still no consensus on the early inguinal lymph node dissection (eILND) of T1G2 or T1aG2. In this study, we investigated the peculiarities of penile cancer T1G2 and T1aG2 to assess the necessity of eILND for this subgroup.

Methods: A total of 144 patients had been treated for penile squamous cell carcinoma with primary tumor excision and early bilateral inguinal lymphadenectomy in my institution from January 2002 to March 2017, thus, 53 patients definitely diagnosed as T1G1 or T1G2 were included in this study. According to the recent guideline, T1aG1 and T1aG2 were even researched. The chi-square test and the Fisher exact test were used to compare categorical variables. Survival were retrospectively analyzed by the Kaplan-Meier method and assessed by log-rank tests.

RESULTS: Among 53 patients, the proportion of positive lymph node of T1G2 was 68.8%, which was significantly higher than T1G1 (18.9%, P=0.001). Then we analyzed the patients of clinically node-negative patients (cN0), micro metastatic disease occurred in T1G2 was 50% but in T1G1 was 14.8%, which also reached statistical significance (p=0.043). According to the recent guideline, T1aG1 and T1aG2 had been further analyzed. As the risk for lymphatic spread, T1aG2 was 44.4% while only 4.5% of T1aG1 was found Inguinal lymph node metastasis, significant differences of which were also reached (P=0.017). In an addition, Survival Curve had been demonstrated but no statistical differences found between T1G1 and T1G2, as the same result also existed in the cohort of T1aG1 and T1aG2, all of which revealed a strong proof of therapeutic benefits of eILND.

CONCLUSIONS: The option of a surveillance strategy is not applicable to patients of T1G2 or T1aG2, eILND should be highly recommended for this subgroup to achieve the most therapeutic benefits.

Background

Penile cancer is a rare but highly malignant tumour, the most common histologic subtype of which is squamous cell carcinoma (SCC). The incidence in Europe and the United States ranges between 0.3 and 1.8 per 100,000 men [1], while it occurs in higher rates in the developing countries. The management of regional lymph nodes is significant and decisive for long-term patient survival. Early inguinal lymphadenectomy in clinically node-negative patients is far superior for long-term patient survival compared to therapeutic lymphadenectomy when regional nodal recurrence occurs [2]. For a long time, there is still no consensus on the early inguinal lymph node dissection (eILND) of T1G2. In earlier times, the European Association of Urology (EAU) guidelines recommend an eILND in patients with T1G2–3 tumours and surveillance can only be offered in patients with pTis and pTa penile cancer and with the appropriate caveats in pT1G1 tumours [2]. Conversely, in North America an eILND is more often used only in patients of tumours > T1G2[3] .At present, the 2009 version of TNM staging manual was used instead of earlier version, T1 has been further divided into T1a and T1b according to whether the presence of lymphovascular invasion or the degrees of differentiation. The necessity of eILND for T1aG2 remains

controversial. To our knowledge, there still lack of studies on the peculiarities of T1G2 especially T1aG2 according to the recent guideline.

To assess the characteristics of the penile cancer of T1G1 and T1G2, we retrospectively studied the cohort of our institution, which all of patients were operated by standard surgery by two sophisticated surgeons. With the help of a dedicated pathologist, we even analyzed the differences of T1aG1 and T1aG2 based on the recent guideline, which had not been researched before.

Methods

Patients And Treatment

Between January 2002 and March 2017, there were 144 Chinese patients treated for penile carcinoma of SCC in my institution. Clinical staging consisted primary tumor evaluation, inguinal palpation to assess the presence or absence of identifiable lymph nodes, and computerized tomography of the chest, abdomen and pelvis.

Since the majority of patients with penile cancer in China are of low socioeconomic class which makes regular follow up examination difficult. We regularly perform the partial/total penectomy simultaneously with bilateral inguinal modified lymphadenectomy in most cases to assure adequate treatment (except those Ta/Tis disease or M1). All of the surgeries are performed by 2 sophisticated surgeons and the boundary, technology and criteria of inguinal lymphadenectomy of the operation were complied with the rules reported before [4]. The SCC guideline of the version of 2002 classification system had been used in my institution before 2010, which defined a T1 penile carcinoma as a tumor that invaded sub epithelial connective tissue but not corpus spongiosum or cavernosum or other structures like urethra or prostate. A G2 differentiation described an ‘intermediate’ differentiated tumor, which meaned that it was neither ‘well differentiated’ (G1) nor ‘poorly differentiated’ or ‘anaplastic’ (G3) [5]. Since 2011, we have adopted the version of 2009 SCC guideline, in which T1 has been further subclassified into T1a and T1b on the basis of whether the presence of lymphovascular invasion and the degrees of differentiation [6]. Owing to my single institution of sophisticated surgeons, standard surgery, comprehensive clinical data, in the joint efforts of a dedicated pathologist, all tumors were restaged based on the recent guideline classification. In order to have consistent and better comparable results, the following inclusion criteria were strictly implemented: (1) Only patients pathologically confirmed penile squamous cell carcinoma as T1G1 or T1G2 were included; (2) Bilateral inguinal LN dissection with ≧ 8 LNs were removed; (3) Primary tumors and their metastases were available to be further stratified by the recent guideline [6]. (4) The patient had no distant metastasis or chemotherapy/radiotherapy before the surgery. (5) ILND was operated definitely within six weeks after primary tumors removed in other therapy centers. Thus, we identified 64 patients with T1 penile cancer, of which 53 patients were included in this study and had disease classified according to the 2009 version of SCC guideline [6] as pN0—35(66%), pN1—7 (13.2%), pN2—5 (9.4%)and pN3—6(11.3%).

The follow- up was started from date of surgery to the date of death or last follow-up. All the date were obtained on the basis of medical charts, outpatient clinic records and when necessary through contact with the patient's family. The strategy of Long-term follow – up is that every 3 month for the first 2 years after surgery, every 6 moth during the 3rd -4th years and then once yearly thereafter. The follow-up deadline was April 2018. The study protocol has been approved by the ethics committee.

Statistical analysis

Categorical variables were compared using the chi-square test and the Fisher exact test. CSS rates were calculated by the Kaplan-Meier method as time from the date of ILND to the date of cancer-specific death, and assessed by log-rank tests. Patients who were alive at the end of the study were censored at the last follow-up. All reported P values are two-sided, with P□0.05 indicating statistical significance. All statistical tests were performed with SPSS 19.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

Among these 144 Chinese patients treated for penile carcinoma of SCC with eILND in our institution, 64 patients were diagnosed as T1 SCC in the end by histopathological specimens after surgery. Excluding 6 patients whose primary tumor excision elsewhere was not available, 3 patients only consented to treatment of the primary lesion, 2 patients with higher grade(G3,G4), the remaining 53 patients were included in our study. The median age of all enrolled 53 patients was 52 (27–82) years old and the ratio of postoperative patients with the positive lymph node is (34%). The median number of LNs retrieved of each side was 12 (4–27). According to the latest guideline [6], we further sub-classified the T1 into T1a and T1b. All results of examination of the histopathological specimens after surgery were reassessed by a dedicated pathologist. The clinic pathologic characteristics and analyzations of the 53 patients with T1 penile cancer are listed in Table 1.

Table 1
Characteristics and outcomes of the 53 patients with T1 penile cancer

	pN0	pN(+)				P
			pN1	pN2	pN3	
Grade, n (%)						0.001
G1	30(81.1)	7(18.9)	3(8.1)	1(2.7)	3(8.1)	
G2	5(31.3)	11(68.8)	4(25)	4(25)	3(18.8)	
LVI, n (%)						0.005
Absent	33(75.0)	11(25.0)	5(11.4)	3(6.8)	3(6.8)	
Present	2(22.2)	7(77.8)	2(22.2)	2(22.2)	3(33.3)	0.032
cLN						
Absent(cN0)	28(75.7)	9(24.3)	5(13.5)	4(10.8)	0(0)	
Present(cN1)	7(43.8)	9(56.3)	2(12.5)	3(18.8)	4(25)	
cN0						0.011
T1G1	23(88.5)	3(11.5)	2(7.67)	1(3.83)	0	
T1G2	5(45.5)	6(54.5)	3(27.25)	3(27.25)	0	
Based on recent guideline[6]						0.017
T1aG1	21(95.5)	1(4.5)	1(4.5)	0(0)	0(0)	
T1aG2	5(55.6)	4(44.4)	2(22.2)	2(22.2)	0(0)	

Follow Up And Outcomes

Median followup was 45 months (range 10 to 137). At followup, 45 patients survived and 8 died of the disease. The patients with pN (+) disease were regularly received adjuvant chemotherapy of 5-fluorouracil and cisplatin postoperatively according to European guideline and the others were advised be closely followed up [2]. Radical Pelvic lymphadenectomy was not performed in our therapeutic center for the reason of debatable therapeutic benefit and serious morbidity [7, 8]. There were 8 recurrences observed during followup. Mean time to recurrence after lymphadenectomy was 9 months (range 3 to 15). The locations of recurrence were most on the incisal margin of penis(3 on penis ,2 in pelvis, 2 on bones, 1 in lungs) while there was no inguinal recurrence in our cohort. To demonstrate the differences of long-term survival between the T1G1 and T1G2, Survival Curve had been used and no statistical difference was found in these two cohorts. The same result was also shown between the T1aG1 and T1aG2.(Fig. 1.A.B)

Disscussion

The management of regional lymph nodes is decisive for long-term patient survival. In clinically node-negative patients (cN0), micrometastatic disease occurs in about 25% of cases and is related to the local tumour stage and grade. The delay of the lymphadenectomy procedure is associated with an increased risk of failure. Also, many authors emphasize that lymphadenectomy should be performed as soon as possible after treating the primary lesion on the penis [11–13]. Nevertheless, owing to be afraid of surgical complications or the risk of overtreatment, the studies of necessity of early inguinal lymphadenectomy operated on the patients of T1G2, especially T1aG2 are still deficient.

To the best of our knowledge, vast majority of previous studies on this issue were retrospective and none randomized controlled trials was addressed or under way. Besides, various local therapies of penile cancer, relatively few or even none ILND cases to the whole cohort, not long enough follow-up time, lack of the essential information or no pathological external validation, all of which made the nature of this issue confused and may hinder to catch significant differences. In a serious of 20 patients of T1G2 from 5 different centers, Naumann et al. demonstrated the risk for lymphatic spread to be 50% [14]. These data are similar to a sub-analysis of a Dynamic Sentinel Node Biopsy (DSNB) series published by Leijte et al. [15]. Whereas, B.Schlenker et al. reported 28.9% positive lymph nodes with a cohort of 38 cases [16]. The similar result (25%) was declared in another study include only 4 patients [17]. Confusedly, some authors published no positive lymph nodes in the T1G2 subgroup in their studies [18, 19]. In a more recent research, Rodolphe Thuret et al. had studied 655 T1 patients of cN0 who only underwent primary tumor excision but not performed an eILND relying on the database of Surveillance, Epidemiology, and End Results (SEER) [20]. In that study, the 5-year caner-specific mortality of T1G2 was 10%, which was significantly higher than T1G1 (2.6%) while the 5-year other-cause mortality of T1G2 was even 27.3%, still the benefit of eILND in T1G2 was unclear. In our opinions, there were some limitations in that study. Firstly, the proportion of excisional biopsy of primary lesion was as high as 32.4%, while biopsies of penile caner may lead to the risk of under staging a T2 or T3 tumor since the deepest point of invasion, histologic grade, and risk factors like vascular invasion were reported to be incorrect in 30% – 91% of cases [21]. Additionally, as all of patients in that cohort without an eILND, their results could not compare with a series that did undergo an eILND with no caution, especially if the eILND was performed in the context of lymph node metastasis. Referring to guidelines in this subgroup, there are no North American recommendations supporting the need for an eILND, whereas the EAU SCC treatment guidelines still do recommend an eILND being necessary to these patients [20].

In our study, the partial/total penectomy and early bilateral inguinal modified lymphadenectomy ensured the most therapeutic benefits of these patients. Also, the unified primary lesion excisions guaranteed the accuracy of pathological staging. Additionally, the median number of LNs retrieved of each side was 12, more than the requested 8 removed LNs. By performing standardized lymphadenectomy, separately submitting LN packets and with a dedicated pathologist reassessing the specimen, we obtained accurate clinical and pathologic characteristics. The differences of T1aG1 and T1aG2 according to the latest guideline even could be analyzed, which hadn’t been researched before. In this cohort, the proportion of

positive lymph node of T1G2 was 68.8%, which was significantly higher than T1G1 (18.9%). We further analyzed the patients of clinically node-negative patients (cN0), micro metastatic disease occurs in T1G2 was 50% but in T1G1 was 14.8%, which also reached statistical significance. According to the latest guidelines, significant differences were reached as the risk for lymphatic spread of T1aG2 was 44.4% while only one 4.5% of T1aG1 was found inguinal lymph node metastasis. In an addition, Survival Curve had been demonstrated but no statistical differences found between T1G1 and T1G2 and the same result also existed in the cohort of T1aG1 and T1aG2, all of which revealed a strong proof of eILND's therapeutic benefit.

Up to 68.8% of patients with T1G2 and 44.4% of patients with T1aG2 definitely harbored lymph node metastasis, lymphadenectomy should be highly recommended, which was also mentioned in the EAU guidelines for this subgroup. The option of a surveillance strategy recommended by AJCC was not applicable to these patients, since the great potential risks of a definite worsening of the prognosis in case of regional recurrence far outweighed the non–life-threatening risks of lymphadenectomy. At present, modified inguinal lymphadenectomy which reduces the morbidity and preserves the therapeutic benefit compared to radical ILND has been recommended in patients who have high-risk primary penile tumours and clinically negative groins. As the sensitivity of dynamic sentinel node biopsy (DSLNB) is variable, this technology has only been extensively studied by a few large specialized European centers but failed to gain widespread implementations in outside [22, 23]. Fortunately, in the recent years, some minimally invasive technologies have emerged like laparoscopic surgery and even robot-assisted techniques are under investigation which could further reduce patient morbidity caused by lymph node dissection and better diagnose or treat those patients who will most benefit from lymphadenectomy.

There are some limitations to our study we have to acknowledge. Firstly, it was an uncontrolled, retrospective study. With unified criteria of surgery, a dedicated pathologist reassessing the specimen, relatively new incidences (all surgeries were implemented after 2002), comprehensive clinical and pathological data, we had minimized the potential flaws of a retrospective research. Secondly, a relatively small number of T1G2 patients were included in this study. Nevertheless, most of our cohort had a long followup and the stage of primary lesion and the status of lymph node metastasis were definitely clarified by routinely standard surgical procedures. To our knowledge this is the first study in the literature to specifically concentrate on the penile cancer of T1aG1 and T1aG2 in detail. Additionally, due to socioeconomic factors, the close surveillance and appropriate caveats in the patients of T1G1 SCC tumours are unavailable in our country. Bilateral inguinal modified lymphadenectomy was offered to this subgroup to achieve the most therapeutic benefits. Lastly, though the concept of T1G2 has been updated by the latest SCC guideline, owing to such low-prevalence disease, lack of enough awareness of operative methods or decision-making strategies, ambiguity and deficiency of pathological diagnosis, a number of therapy centers as far as we know still adopt earlier version of SCC guideline in our country especially in some rural areas. In view of above, we have investigated T1G2 and T1aG2 respectively and patients with this subset should be more carefully managed.

Conclusion

As the risk for lymphatic spread, T1G2 is significantly higher than T1G1, which is same in T1aG2 and T1aG1. The option of a surveillance strategy is not applicable to patients of T1G2 or T1aG2 and eILND should be routinely performed in this subgroup to achieve the most therapeutic benefits.

Abbreviations

eILND early inguinal lymph node dissection

SCC squamous cell carcinoma

EAU European Association of Urology

DSLNB sensitivity of dynamic sentinel node biopsy

Declarations

Ethics approval and consent to participate: The ethic of this manuscript is approved by the ethics committee of Guangzhou Medical University Affiliated Cancer Hospital. Ethics board approval number is (2014)□□□141□. All human subjects provided written informed consent with guarantees of confidentiality.

Consent for publication: Not applicable

Availability of data and material: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: No potential conflict of interest relevant to this article was reported.

Funding: Not applicable.

Authors' contributions: Dr Jing Li is in charge of conception and design, drafting of the manuscript; Dr Bin Wang is in charge of revision and supervision of the manuscript; Dr Zai-shang Li is in charge of acquisition and analysis of data; Dr Jian-an Yang is in charge of conception and design, statistical analysis;

Acknowledgements: Not Applicable.

References

1. Curado MP, Edwards B, Shin HR, et al. Cancer Incidence in Five Continents. Lyon: IARC Scientific Publications No. 160; 2007.
2. Pizzocaro G, Algaba F, Horenblas S, et al. European Association of Urology (EAU) guidelines group on penile cancer.Eur Urol 2010 ; 57 : 1002–123.

3. National Cancer Institute, US National Institutes of Health. Availableat:http://www.cancer.gov/cancertopics/pdq/treatment/penile/HealthProfessional.Accessed May 2010.
4. Yao K, Tu H, Li YH, et al. Modified technique of radical inguinal lymphadenectomy for penile carcinoma: morbidity and outcome. J Urol. 2010;184:546–52.
5. Sobin LH, Wittekind C. TNM Classification of Malignant Tumors. 6th ed. Philadelphia: Wiley-Liss; 2002.
6. Edge SBBD, Carducci MA, Compton CC. AJCC Cancer Staging Manual. New York: Springer; 2009. pp. 447–56.
7. Leone A, Diorio GJ, Pettaway C, et al. Contemporary management of patients with penile cancer and lymph node metastasis. Nat Rev Urol. 2017 Jun;14(6):335–47.
8. Spiess PE, Hernandez MS, Pettaway CA. Contemporary inguinal lymph node dissection: minimizing complications. World J Urol. 2009;27:205–12.
9. Bandieramonte G, et al. Peniscopically controlled CO2 laser excision for conservative treatment of in situ and T1 penile carcinoma: report on 224 patients. Eur Urol. 2008;54:875. http://www.ncbi.nlm.nih.gov/pubmed/18243513.
10. Colecchia M, et al. pT1 penile squamous cell carcinoma: a clinicopathologic study of 56 cases treated by CO2 laser therapy. Anal Quant Cytol Histol. 2009;31:153.
11. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. 2. The role and technique of lymph node dissection. BJU Int. 2001;88:473–83.
12. Kroon BK, Horenblas S, Lont AP, Tanis PJ, Gallee MP, Nieweg OE. Patients with penile carcinoma benefit from immediate resection of clinically occult lymph node metastases. J Urol. 2005;173:816–9.
13. Wiechno P, Kalinowski T, Itrych B, et al. Prognostic factors in patients undergoing lymphadenectomy for squamous cell carcinoma of the penis. Urol Int. 2014;92(2):194–201.
14. Naumann CM, Alkatout I, Al-Najar A, et al. Lymph node metastasis in intermediate-risk squamous cell carcinoma of the penis. BJU Int. 2008;102:1102–6.
15. Leijte JA, Kroon BK, Valdes Olmos RA, et al. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. EurUrol. 2007;52:170 – 7.
16. Schlenker B, Tilki D, Gratzke C,et al. Intermediate-differentiated invasive (pT1 G2) penile cancer—oncological outcome and follow-up. Urol Oncol. 2011 Nov-Dec;29(6):782–7.
17. Solsona E, Iborra I, Rubio J, et al. Prospective validation of the association of local tumor stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. J Urol. 2001;165:1506–9.
18. Hegarty PK, Kayes O, Freeman A, et al. A prospective study of 100 cases of penile cancer managed according to European Association of Urology guidelines. BJU Int. 2006;98:526 – 31.

19. Alcides Chaux. Risk Group Systems for Penile Cancer Management: A Study of 203 Patients With Invasive Squamous Cell Carcinoma. Urology. 2015 Oct;86(4):790–6.
20. Thuret R, Sun M, Abdollah F, Budaus L,et al. Competing-risks analysis in patients with T1 squamous cell carcinoma of the penis. BJU Int. 2013 Apr;111(4 Pt B):E174-9.
21. Velazquez EF, Barreto JE, Rodriguez I, et al. Limitations in the interpretation of biopsies in patients with penile squamous cell carcinoma. Int J Surg Pathol. 2004;12:139–46.
22. Leone A, Diorio GJ, Pettaway C,et al. Contemporary management of patients with penile cancer and lymph node metastasis. Nat Rev Urol. 2017 Jun;14(6):335–47.
23. Protzel C, Alcaraz A, Horenblas S, et al. Lymphadenectomy in the Surgical Management of Penile Cancer. Eur Urol. 2009 May;55(5):1075–88.

Figures

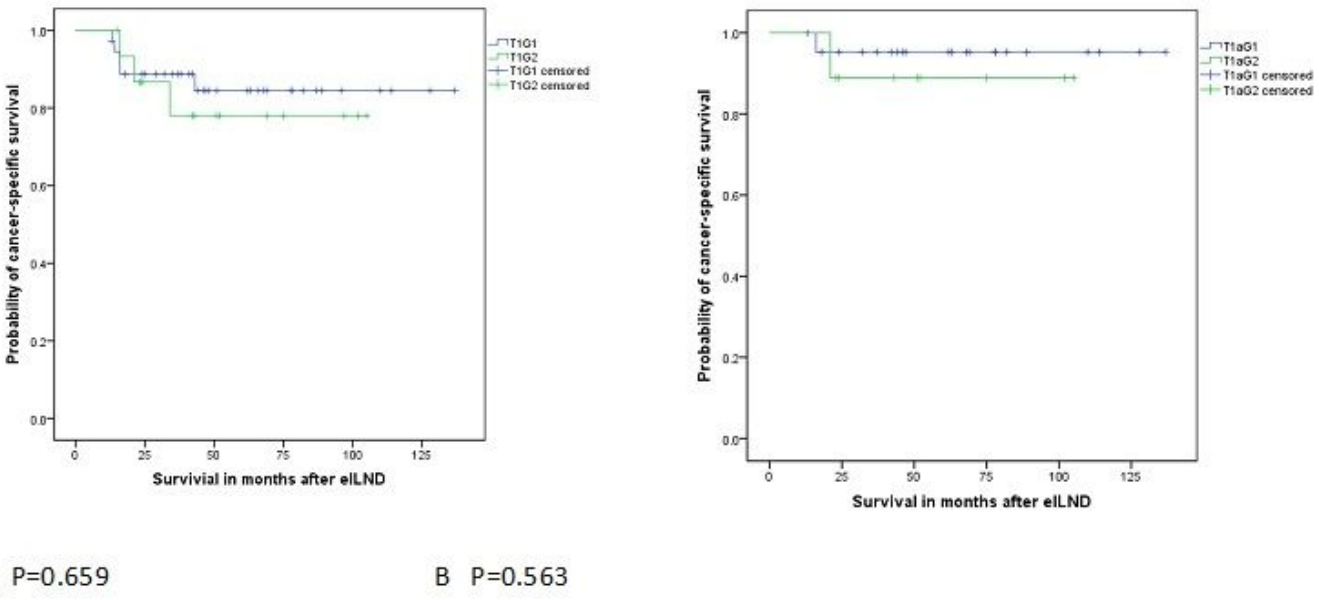

Figure 1

A. Cancer-specific survival (CSS) probabilities of T1G1 and T1G2. B. Cancer-specific survival (CSS) probabilities of T1aG1 and T1aG2