

Incidence and Magnitude of Complications Related to Modified Inguinal Lymph Node Dissection for Patients with Penile Squamous Cell Carcinoma

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Abstract

Objective: We investigated complications related to modify inguinal lymph node dissection (ILND) for penile squamous cell carcinoma (PSCC). Modified ILND was performed for poor performance status, groins with contralateral impalpable nodes in unilateral palpable nodes, and conventional indications.

Methods: From April 2011 to November 2016, modified ILND was performed at the Yokohama City University Medical Center and its hospital for 16 groins of 12 patients with penile cancer. Seventeen groins of 11 patients who underwent radical ILND were compared (control group).

Results: The mean age of 12 patients at surgery was 67.2 years; mean follow-up was 17.1 months. Skin edge necrosis was observed in 18.8% (3/16) in the modified ILND group. However, the percentage of skin necrosis in the radical ILND group was 94.1% (16/17), which was significantly higher than that in the modified group. The mean duration of drain placement was 6.7 ± 2.6 days, which was significantly shorter than that of the radical ILND group ($p=0.005$). The incidence of leg edema was 25.0%; leg edema had no influence on walking in any case. One patient died of local recurrence and two died of distant metastasis. No locoregional recurrence was reported after modified ILND. The remaining patients survived with no evidence of disease.

Conclusion: Complications occurred less often for modified ILND than for radical ILND. Modified ILND might be a substitute for radical ILND in PSCC patients when dissection of impalpable intermediate-risk or high-risk nodes cannot be performed.

Keywords: Penile cancer; Modified inguinal lymph node dissection; Radical inguinal lymph node dissection; Complication; Leg edema; Skin edge necrosis; Prognosis

Introduction

Most cases of urological cancer with regional lymph node metastasis have a poor prognosis. However, penile squamous cell carcinoma (PSCC) can be surgically treated despite the presence of inguinal lymph node metastasis [1]. Therefore, inguinal lymph node dissection (ILND) is an important therapeutic procedure for patients with PSCC. However, few urologists have had the opportunity to perform this procedure because of the rarity of the disease. Furthermore, complications associated with radical ILND are frequent [1,2]. Therefore, this procedure is not performed regularly in Japan. Fraley et al. first reported modified ILND in 1985 [3]. Thereafter, D'Ancona and colleagues reported that modified ILND reduced the incidence of complications [4] and was effective as a staging procedure for T2-3 PSCC. Currently, according to the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines for penile cancer, modified ILND is recommended for patients with intermediate-risk or high-risk tumors and impalpable nodes [5,6]. We used this procedure for patients with a poor general status or with contralateral impalpable nodes in the unilateral palpable

node of the groin, and for patients with conventional indications. We reviewed our experience with modified lymphadenectomy at the Yokohama City University Medical Center to determine the incidence and magnitude of complications related to surgery.

Materials and Methods

The Ethical Review Board committee of the Yokohama City University Medical Center (Yokohama, Japan) approved the study protocol. Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

From April 2011 to November 2016, we performed modified ILND at the Yokohama City University Medical Center and its associated hospital for 16 groins of 12 patients with penile cancer. As controls, we included 17 groins of 11 patients who underwent radical ILND. We determined the indication criteria for modified ILND as follows: (1) intermediate-risk or high-risk tumors and impalpable nodes according to the EAU and NCCN guidelines [5,6]; (2) worsening general status; and (3) radical ILND performed for groins with unilateral palpable nodes when a contralateral impalpable node existed. In this situation, modified ILND was performed for groins with no palpable nodes.

The technique of radical ILND is designed to cover the following limits: superiorly, from the superior margin of the external ring to the

anterior superior iliac spine; laterally, from the anterior superior iliac spine, extending 20 cm inferiorly; and medially, from the pubic tubercle to 15 cm down the medial thigh. The dissection plane is deepened laterally, through the fascia overlying the sartorius muscle, and medially, through the fascia covering the adductor longus muscle. At the apex of the femoral triangle, the femoral artery and vein are identified. The procedure involves skeletonizing the femoral vessels. The sartorius muscle is detached from its origin at the anterior superior iliac spine, transposed medially over the femoral vessels, and sutured to the inguinal ligament [7-9]. Modified ILND was designed to provide staging information and therapeutic benefits similar to those of radical ILND but with less morbidity. Therefore, in contrast to conventional methods, we preserved the saphenous vein as much as possible to prevent lymphedema of the legs. A 5-cm skin incision was made 2 cm below the inguinal arcade, along the femoral vessels. The adipose and lymphatic tissues below the Scarpa fascia were resected en bloc with the adductor longus muscle as the medial border, the medial surface of the femoral and saphenous veins as the lateral border, and the inguinal arcade as the superior border, thereby forming a triangle [4,10]. Modified ILND can be performed with frozen-section examination of the specimen; if the results are positive, then the procedure can be converted to radical ILND, except in cases of poor performance status. The corresponding author (Y.Y.) participated in all surgeries along with another surgeon or assistant. For all patients, modified or radical ILND was performed at the same operative time as penectomy, except when inguinal lymph node metastasis was detected after initial penectomy. After ILND, pressure was applied to the wound with rounded gauze for 2 days. Antibiotic prophylaxis with cefazolin was introduced during induction of anesthesia and continued for 3 days. Low-molecular-weight heparin was administered as prophylaxis for deep venous thrombosis and maintained for 48 hours. Extremity compression hose were prescribed for all patients. Two 9-Fr J-VAC suction reserver/blake silicon drains (Ethicon Inc., Somerville, NJ, USA) were used for radical ILND, whereas one was used for modified

ILND. Drains were removed when the drain discharge volume decreased to less than 20 mL/day. We investigated the incidence and magnitude of complications related to modified ILND, the duration of drain placement, and cancer-specific survival after ILND. Regarding the magnitude of skin necrosis, we categorized more than two-thirds of wound necrosis as severe, one-third to two-thirds as moderate, and less than one-third as mild. We categorized leg edema with difficulty walking as severe; leg edema that did not interfere with walking was categorized as mild. Operative time was excluded from the evaluation because the surgical staff members were different during each surgery, except for Y.Y., who provided guidance to the staff members. Clinical staging was performed using the 7th edition of the tumor-node-metastasis system [11].

Statistical Analysis

Statistical values are presented as mean ± standard deviation. A Mann-Whitney U test was used to compare the number of dissected lymph nodes and the duration of drain placement for modified ILND and radical ILND. Differences were considered statistically significant when $p \leq 0.05$. All calculations were performed using the Statistical Package for Social Science software (version 22.0 for Macintosh; SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows patient characteristics. The mean age of the 12 patients was 67.2 years (range, 54-80 years). Modified ILND was performed at the same time as penectomy for 10 patients. Two patients underwent delayed modified ILND because of the detection of inguinal lymph metastasis after initial penectomy. As controls, 17 groins of 11 patients who underwent radical ILND were included. The mean follow-up period was 17.1 months (range, 3.6-54.7 months).

No.	Age	PS	Tumor grade	pT	cN	ILND			Chemotherapy		Recurrence	Prognosis	Cancer-specific survival (months)
						ILND timing	Lt	Rt	Neoadjuvant	Adjuvant			
1	80	2	G1	1a	1	Simultaneous	SLNB	Modified			No	NED	54.7
2	56	0	G3	2	2	Simultaneous	Radical	Modified			Local	DOD	10.6
3	75	1	G2	2	1	Simultaneous	Modified	Modified			No	NED	11.7
4	54	0	G1	2	3	Simultaneous	Modified	Radical	TPFx3	TPFx2	No	NED	25.3
5	62	0	G2	1b	1	Simultaneous	Radical	Modified			No	NED	22.8
6	75	1	G1	2	2	Simultaneous	Modified	Modified	TPFx2		No	NED	15
7	63	0	G1	1b	3	Simultaneous	Radical	Modified	TPFx3		No	NED	12
8	65	1	G3	1b	1	Simultaneous	Modified	Modified			Lung metastasis	DOD	4
9	65	0	G2	1b	0	Simultaneous	Modified	Modified		TPFx2	No	NED	7.5
10	79	0	G2	2	1	Simultaneous	Modified	Radical		TPFx2	No	NED	3.6
11	62	2	G3	1b		Delay (Rt inguinal LN)	Modified	Radical			Lung metastasis	DOD	13.7

12	70	0	G1	1b		Delay (Lt inguinal LN)	Radical	Modified		TPF x2	No	NED	23.8
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PS: performance status; ILND: inguinal lymph node dissection; TPF: combination chemotherapy comprising paclitaxel, cisplatin, and 5-fluorouracil; NED: no evidence of disease; DOD: died of disease; Rt: right; Lt: left; LN: lymph node; pT: Pathological T grade; cN: Clinical N grade; SNLB: Sentinel lymph node biopsy

Table 1: Patient characteristics.

Five patients (8 groins) underwent modified ILND because of their poor general status. Six patients had unilateral palpable inguinal lymph nodes; therefore, radical ILND was performed for groins with palpable nodes, and modified ILND was performed for contralateral groin nodes. One patient underwent bilateral modified ILND because his penile tumor was diagnosed as G2 pT1b and classified as an intermediate-risk tumor. Neoadjuvant chemotherapy was administered to three patients and adjuvant chemotherapy was administered to four patients.

The mean numbers of dissected lymph nodes were 17.0 ± 7.6 and 6.2 ± 3.6 per groin for radical ILND and modified ILND, respectively, and the difference was not statistically significant ($p=0.157$). Although only one patient who underwent modified ILND had positive nodes, conversion to radical ILND was not implemented because of the poor general status. The mean duration of drain placement in the groins that

underwent modified ILND was 6.7 ± 2.6 days, which was significantly shorter than for those that underwent radical ILND (11.1 ± 5.2 days; $p=0.005$). Skin edge necrosis was seen in 94.1% (16/17) of the groins of the patients who underwent radical ILND; however, for modified ILND, skin edge necrosis was seen in 18.8% (3/16). The incidence of leg edema was similar for modified ILND (25.0%) and radical ILND (29.4%). All cases of leg edema were mild and had no influence on walking. Lymphoceles were seen in 23.5% (4/17) and 12.5% (2/16) of the groins that underwent radical and modified ILND, respectively (Table 2). No cases of deep venous thrombosis were noted. During follow-up, one patient died of local recurrence and two died of distant metastasis. Their primary tumor grade was grade 3, and there was no locoregional recurrence reported during follow-up after modified ILND. The remaining nine patients survived with no evidence of disease.

	Number of groins	Number of dissected LN	Complication							Interval for drainage* (days)
			Wound edge necrosis*			Infection	Lymphocele	Leg edema (mild)	Others	
Radical	17	17.0 ± 7.6 (1-28)	Severe 3	Moderate 7	Mild 6	1	4	5	1	11.1 ± 5.2 (6-22)
Modified	16	6.2 ± 3.6 (1-13)	Severe 1	Moderate 2	Mild 0	1	2	4	2	6.7 ± 2.6 (2-10)

*Significant difference. ILND: inguinal lymph node dissection; LN: lymph node

Table 2: Comparison of the number of dissected lymph nodes, incidence, magnitude of complications, and drainage interval between radical and modified ILND for groins

Discussion

Inguinal lymph node metastasis is the strongest prognostic factor for PSCC. The presence and extent of regional inguinal lymph node metastases have been identified as the most important prognostic indicators for determining long-term survival for men with invasive PSCC. Management of inguinal palpable nodes affects prognosis [1,2]. Fine-needle aspiration cytology (FNAC) of palpable nodes is initially recommended because not all palpable nodes are metastatic. ILND is recommended when FNAC results are positive or when lymph node biopsy results are positive but FNAC results are negative [5,6]. When inguinal lymph node metastasis is diagnosed, radical ILND is performed to dissect an area with sufficient size and depth. However, the incidence of radical ILND complications is very high [2]. Furthermore, the learning curve is long due to its infrequent use. This is because of the rarity of the disease. In addition, the surgery itself is time-consuming, which has a negative impact on patient care.

Twenty-five percent of patients with non-palpable inguinal lymph nodes are at risk for micrometastasis [12]. Lymphoscintigraphy showed bilateral drainage in 60%–79% of PSCC cases [13]. A clinical study has shown that the presence of surgically staged positive nodes on one side influenced the incidence of positive nodes on the contralateral side, which varied from 20-60% [14]. Therefore, for cN1

PSCC cases, after accounting for the risk of micrometastasis, we performed radical ILND for groins with palpable nodes. We performed modified ILND rather than sentinel node biopsy for the contralateral groin nodes. In Japan, the population of patients with PSCC is scarce [15]. Therefore, many Japanese urologists rely on their experience rather than treatment guidelines. In our study, although the guidelines recommend FNAC, it was not performed for palpable lymph nodes. Furthermore, despite the recommendation of dynamic sentinel node biopsy or modified ILND for patients with intermediate-risk or high-risk tumors and cN0 PSCC [5,6], very few urologists attempt these procedures because they believe that the impact of ILND complications, especially leg edema and lymphocele, is severe.

For our cases, the incidence of skin edge necrosis was 94.1% for radical ILND and 18.8% for modified ILND. The mean duration of drain placement for modified ILND was significantly shorter than that for radical ILND. The frequency of leg edema was equal for radical and modified ILND. Fortunately, for both radical and modified ILND, the degree of leg edema was mild because of conservation of the saphenous vein. However, in the present study, the incidence of leg edema for those undergoing modified ILND was higher than that reported by others (3-30%) [2]. Therefore, efforts to reduce the frequency of leg edema are necessary. However, the incidence of other complications was equivalent to that reported by others [1,2,5,6].

Overall, there were fewer complications with modified ILND than with radical ILND, as previously reported. A lower incidence of complications makes it possible to prevent worsening of the general condition of the patient after surgery and enables shorter hospitalization periods.

Three patients died of PSCC during follow-up. There was no regional lymph node recurrence after modified ILND. Considering our study results independently, the differences between the two procedure types do not seem to affect prognosis. It may be possible for modified ILND to replace radical ILND for patients presenting with poor general conditions. Frequent follow-up examinations are necessary because many of our patients had short follow-up intervals. However, because 90% of PSCC recurrence occurs within 2 years, it has been speculated that only a few patients die of this cancer type [16].

Our study had some limitations, including its small sample size (16 groins of 12 patients) and retrospective nature. However, PSCC is extremely rare in Japan [15], and there have been limited studies regarding PSCC. Therefore, we believe that collaborative multi-center studies are necessary to determine new treatments for advanced PSCC in Japan.

Conclusion

In this study, the incidence and magnitude of modified ILND complications were less than those of radical ILND, as reported previously. We do not expect modified ILND to have the same therapeutic effect as radical ILND; therefore, we do not recommend this procedure for all cases of inguinal lymph node metastasis. However, when urologists are contemplating surgery for patients with PSCC with palpable inguinal lymph nodes and a poor general status, modified ILND could be a potential substitute for radical ILND for indications other than search for lymph node metastasis in patients with intermediate-risk and high-risk cN0 PSCC.

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Disclosure Statement

The authors declare no conflict of interest. No funding has been received for this work.

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