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ORIGINAL ARTICLE

Effectiveness of intraoperative indocyanine-green fluorescence angiography during inguinal lymph node dissection for skin cancer to prevent postoperative wound dehiscence

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Abstract
Purpose The incidence of postoperative wound dehiscence following inguinal lymph node dissection (ILND) is higher than that in other anatomic regions. To prevent wound dehiscence, intraoperative interventions, such as trimming off the ischemic part of the flap before wound closure based on indocyanine-green (ICG) fluorescence angiography, have been introduced in our institute. This report describes a retrospective clinical study of 17 cases, and the objective of the study was to evaluate the clinical efficacy of intraoperative intervention using ICG fluorescence angiography.
Method A total of 17 patients who underwent ILND for skin cancer between 2009 and 2013 at our institute were reviewed retrospectively, and the significance of variables, including intervention using ICG fluorescence angiography, was evaluated using Fisher's exact test.
Results There were nine cases of wound dehiscence, and two of these cases required a secondary skin graft. Only one case of wound dehiscence developed in the eight patients who underwent intervention based on ICG fluorescence angiography. This procedure was a significant factor influencing the risk of wound dehiscence ($p = 0.003$) in our study.
Conclusion Although this was a small case series, intraoperative intervention based on ICG fluorescence angiography was effective for preventing postoperative wound dehiscence after ILND.

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Keywords Inguinal lymph node dissection · Wound dehiscence · Indocyanine-green fluorescence angiography

Purpose

Lymph node dissection is a standard treatment for skin cancer with regional lymph node metastasis; however, lymph node dissection has been associated with significant postoperative morbidity, including skin flap complications [1]. The incidence of postoperative wound dehiscence following inguinal lymph node dissection (ILND) is higher than that after lymph node dissections in other anatomical regions [1–4]. In a prospective study of melanoma patients undergoing ILND, 53 % had some degree of wound dehiscence (wound dehiscence was defined as poor wound healing with a measured defect of at least 1 cm) [1] The explanations that have been proposed for the increased incidence of wound complications associated with ILND include the greater surface area associated with the dissection, the relatively poor vascular supply to the skin and subcutaneous tissues in that region and the surgical techniques related to the relatively thin skin flaps routinely employed in ILND [1] Wound dehiscence often leads to extended hospitalization, a reduced quality of life and a delayed return to normal activities, despite several novel approaches that have been applied to prevent or to manage wound dehiscence [5–8].

To resolve these issues, we introduced ICG fluorescence angiography during ILND to evaluate the blood flow of the skin flap in September 2011 in the Department of Plastic and Reconstructive Surgery, University of Hokkaido at Sapporo, Graduate School of Medicine. During ILND, the area of ischemic skin around the groin wound just after lymph node dissection was detected based on

ICG fluorescence angiography, and this tissue was excised before wound closure. The aim of this report is to present our surgical intervention during ILND using ICG fluorescence angiography, and to evaluate the impact of our intervention on postoperative wound dehiscence. In addition, we compared our results to those obtained with the use of fluorescein during radical inguinal lymphadenectomy, as were previously reported [9, 10].

Methods

We conducted a retrospective review of 17 lymph node-positive patients with primary skin cancer of the lower extremities, vulva and scrotum who underwent ILND between September 2009 and August 2013 at our institute. For the sentinel lymph node-positive cases (microscopic metastasis), deep groin dissection (DGD) was performed (Fig. 1). DGD was performed using a lazy S incision. The excised tissue from the DGD was the same as that defined by Smith et al., including all lymph nodes, including Cloquet's node, found within a triangular area bounded by the inguinal ligament superiorly, the medial border of the adductor longus medially and the medial border of the sartorius laterally [11]. This tissue includes that reaching deep to the fascia lata within the femoral sheath.

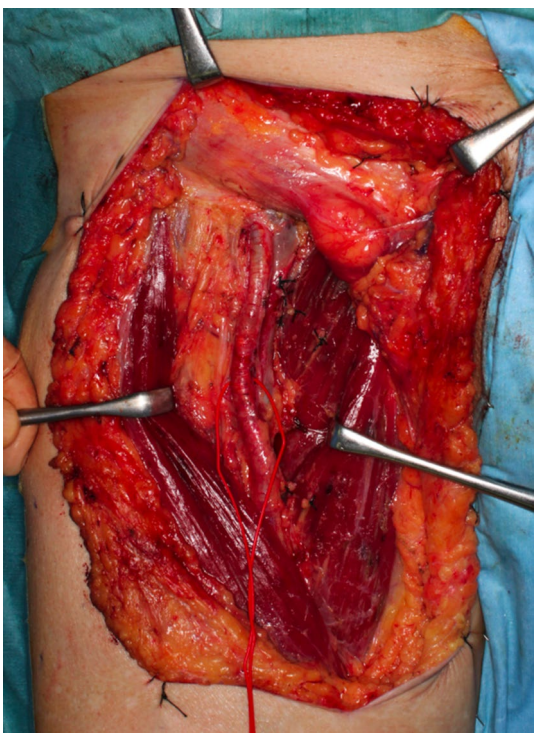

Fig. 1 Intraoperative view immediately after right DGD in case 13

If the lymph node metastasis was palpable disease, combined DGD and pelvic lymph node dissection was performed, which was defined as ilio-inguinal dissection (IID). The excised tissue included the same tissue as DGD, as well as the external iliac and obturator nodes within the pelvis, to which the inguinal nodes drain, and this procedure requires skeletonization of the external iliac vessels [11]. The approach into the iliac and obturator nodes within the pelvis was performed through the same lazy S skin incision as DGD, with the incision extended to the umbilical height on the lower abdomen.

Sartorius flap transposition was performed before the wound closure in both DGD and IID. To prevent wound dehiscence after ILND, the ischemic part of the flap was trimmed off before wound closure. In September 2011, indocyanine-green (ICG) fluorescence angiography was introduced at our institute. This procedure is helpful to clearly distinguish the ischemic and non-ischemic regions of the skin flap. When the sartorius switch was completed, the two flaps were roughly closed using several silk sutures, and the blood supply of the skin flaps was checked by ICG fluorescence imaging with a near-infrared camera system (Photodynamic Eye®, PDE; Hamamatsu Photonics, Hamamatsu, Japan). The light source was a light-emitting diode that emitted light at a wavelength of 760 nm, and the detector was a charge-coupled device (CCD) camera with a filter used to filter out light with a wavelength of <820 nm. The fluorescence signals were sent to a digital video processor to be displayed on a TV monitor in real time [12].

The ICG solution was gently injected from a peripheral venous route. The solution contained 25 mg of ICG dye (Diagnogreen, Daiichi-Sankyo Company, Tokyo, Japan) in 10 ml of saline, and the total amount of injected dye was 1 ml. After binding to plasma protein, ICG fluoresces when illuminated with near-infrared light. ICG absorbs light in the near-infrared spectral range, with a maximum at 805 nm, and emits fluorescence with a maximum at 835 nm. These absorption and emission qualities lie in the "optical window" of the skin, where the absorption of intrinsic chromophores like hemoglobin and water is low. Thus, ICG fluorescence occupies a "biological spectral window" that allows excellent visualization of deep structures in the living body. The fluorescence sequentially shows the blood flow as the dye passes through the microcirculation [12].

Approximately 1–3 min after the injection of the ICG, the blood flow of the skin flap was confirmed by ICG fluorescence imaging as a white stain. Areas of non-fluorescence were marked using a pen (Figs. 2, 3). To prevent postoperative flap necrosis or wound dehiscence, the edge of the skin flaps with non-fluorescence was trimmed off, while preserving the other parts of skin flaps with fluorescence.

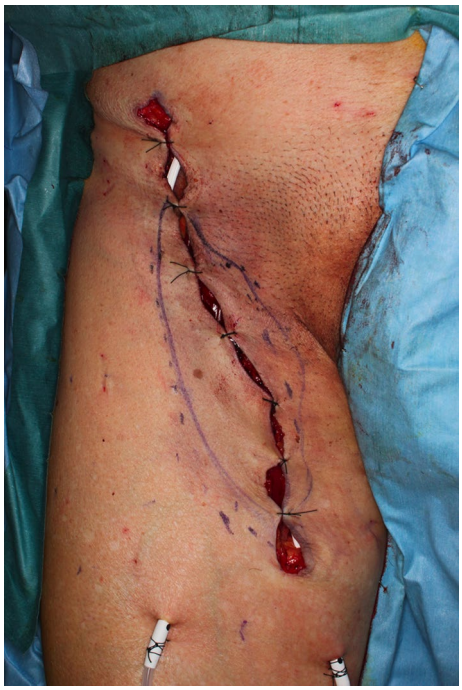

Fig. 2 In case 13, after the sartorius muscle was transferred, both the lateral and medial flaps were roughly closed using several silk stitches. The fluorescence signals displayed on a TV monitor of PDE, 3 min after ICG injection, were marked using a *purple pen*

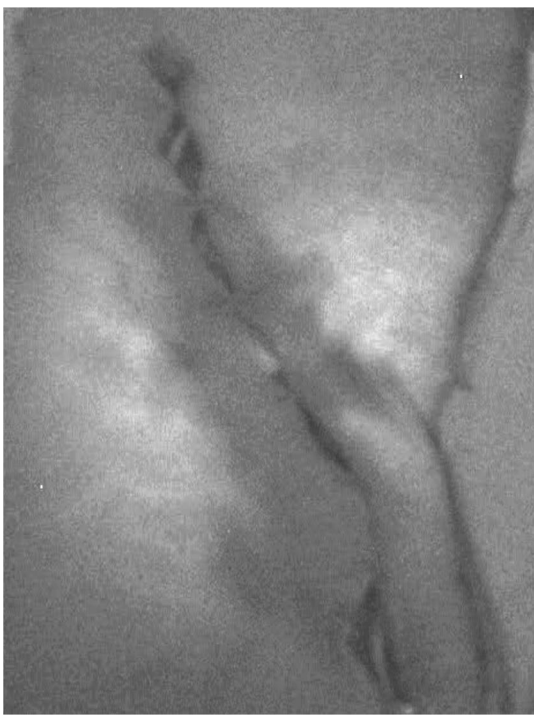

Fig. 3 In case 13, the fluorescence signals displayed on a TV monitor of PDE, 3 min after ICG injection. The fluorescence sequentially shows the illumination of the blood flow as the dye passes through the microcirculation. The edges of the flaps lack any fluorescence, and they were thus trimmed off at the line marked with a *purple pen*

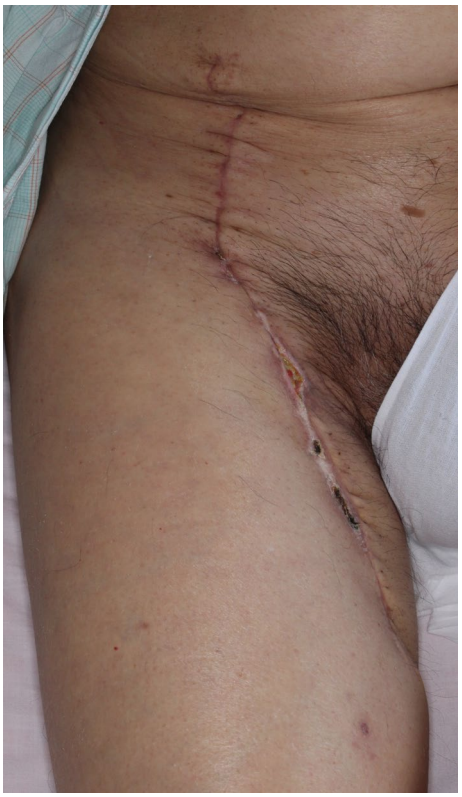

Fig. 4 There was no necrosis or break down measuring more than 1 cm width of the remnant skin flap postoperatively at 3 weeks after DGD in case 13

Postoperative wound dehiscence was defined as poor wound healing with a measured defect or necrosis of at least 1 cm in width, identified as that lasting 3 weeks or longer after ILND (Figs. 4, 5). The patients were reviewed to evaluate the significance of variables associated with postoperative wound dehiscence, including the age, sex and body mass index (BMI) of the patient, the level of dissection (DGD or IID) and whether or not there was intervention based on the intraoperative blood flow evaluation using ICG fluorescence angiography. Because of the small number of samples, we performed Fisher's exact test for a 2×2 contingency table. Fisher's exact test is a bivariate analysis used to determine if there are non-random associations between two categorical variables (with or without angiography, and with or without skin necrosis). The p value of Fisher's exact test is accurate even for small samples. Results with a value of $p \leq 0.05$ were considered to be statistically significant.

Results

Table 1 summarizes the clinical and pathological data for our patients. Eight of the 17 patients were male, and nine

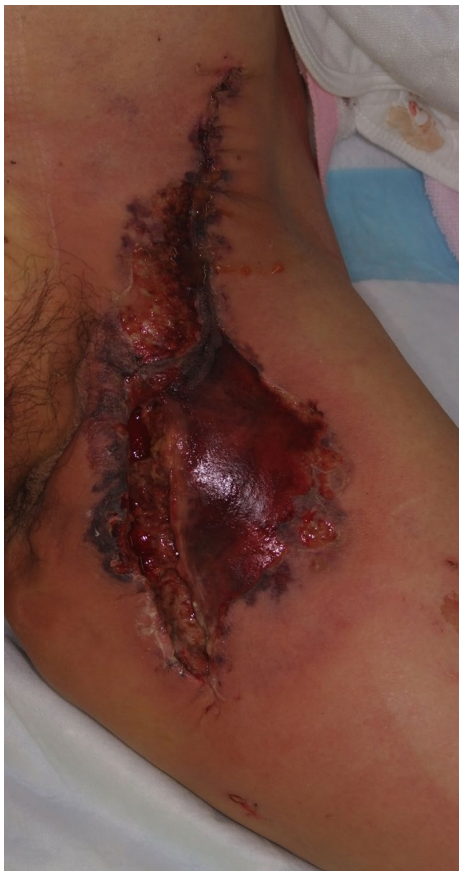

Fig. 5 The necrosis or break down measuring more than 1 cm width of the remnant skin flap in Case 2 is presented. Additional debridement and skin graft was required

patients were female. The median age of the study population was 71 years, and the average age was 68.3 years (range, 43–84 years). The pathological diagnosis of 12 patients was melanoma, that of two patients was sebaceous carcinoma, two patients had squamous cell carcinoma and one patient presented with extra-mammary Paget's disease. The average BMI was 22.8 kg/m^2 (range, 18.1–28.5). DGD was performed in nine cases, and IID was performed in eight cases. Nine cases presented with wound dehiscence lasting at least 3 weeks after ILND (53 %), and two of the cases required secondary skin grafts 2–3 weeks after ILND. The ischemia of the flaps was evaluated with intraoperative ICG fluorescence angiography in eight cases treated after September 2009, and only one of these cases developed postoperative wound dehiscence.

The results of the univariate analyses of the clinical characteristics of the patients and the surgical procedure affecting postoperative wound dehiscence are presented in Table 2. Our 17 cases were divided into two groups according to age (<70 years old and ≥70 years old), sex (male or female), BMI (≥23 kg/m^2 or <23 kg/m^2), the level of dissection (DGD or IID) and the evaluation for flap ischemia (with or without ICG angiography), and the differences in postoperative wound dehiscence were analyzed for statistical significance. The age, sex, BMI, and level of dissection were not identified as factors influencing wound dehiscence in our cases, but intervention based on intraoperative ICG fluorescence angiography was a factor that significantly influenced the risk of wound dehiscence ($p = 0.003$).

Discussion

The incidence of postoperative wound dehiscence following inguinal lymph node dissection (ILND) is higher than that of nodal dissections in other anatomical regions. Sharon reported that obesity is an adverse risk factor for 30-day wound complications that can significantly increase postoperative costs, and this is also likely the case for advanced disease [1]. A BMI ≥30 kg/m^2 increased the risk for wound complications in their cases. In our study, the average BMI was 22.8 kg/m^2 (range, 18.1–28.5), and BMI was not identified as a factor influencing wound dehiscence.

Novel treatment approaches were reported to prevent the development of wound dehiscence after ILND as a postoperative morbidity. These strategies included preservation of the fascia lata and saphenous vein, primary flap reconstruction, the application of topical negative pressure and the application of a gelatin matrix thrombin tissue sealant [1] to prevent wound dehiscence [5–8]. However, the most reliable procedure to prevent wound dehiscence after ILND was trimming off the ischemic part of the flap before wound closure. To determine the proper trimming line on the flap, an evaluation of the blood supply of the flap is important. Surgeons generally decide on this line depending on the flap color and bleeding from the edge of the flap. In addition to these macroscopic findings, ICG fluorescence imaging was very useful to more clearly distinguish the ischemic and non-ischemic areas.

ICG was first used to evaluate perfusion by Flower and Hochheimer in 1976 [13]. Since then, a large number of experimental and clinical studies have been published on ICG imaging. Due to the great emphasis on the blood supply in plastic and reconstructive surgery, a significant number of these experimental and clinical studies have been centered on plastic surgical procedures [14]. The use of fluorescence in radical inguinal lymphadenectomy for flap blood evaluation was reported previously [9, 10], with most of these studies using sodium fluorescein dye, where the excitation occurs at 494 nm and emission at 521 nm. We introduced ICG imaging for ILND, rather than sodium fluorescein dye, for the following reasons: (1) Near-infrared light penetrates deeper into the skin, so the excitation light induces fluorescence from blood vessels within the deep dermal plexus and subcutaneous fat, instead of only the superficial dermis (as with fluorescein).

Table 1 Patient summary

Case	Sex	Age	Pathological diagnosis	Location of primary tumor	Inguinal lymph node dissection	BMI	Intervention based on intraoperative ICG fluorescence angiography	Wound dehiscence persisting until 3 weeks after dissection	Secondary skin graft
1	M	71	Sebaceous carcinoma	Thigh	DGD	22.9	−	+	−
2	F	72	Squamous cell carcinoma	Thigh	IID	23.1	−	+	+
3	M	74	Extra-mammary Paget's disease	Scrotum	DGD	25.3	−	+	−
4	F	63	Malignant melanoma	Foot	IID	18.1	−	+	−
5	F	73	Malignant melanoma	Foot	IID	20.5	−	+	+
6	M	65	Malignant melanoma	Foot	DGD	22.2	−	−	−
7	F	81	Malignant melanoma	Leg	DGD	25.8	−	+	−
8	F	56	Malignant melanoma	Leg	DGD	22.2	−	+	−
9	F	54	Malignant melanoma	Vulva	DGD	21.7	−	+	−
10	F	66	Sebaceous carcinoma	Thigh	IID	20.2	+	−	−
11	F	74	Malignant melanoma	Thigh	IID	24.3	+	−	−
12	M	71	Malignant melanoma	Foot	IID	24	+	−	−
13	M	78	Malignant melanoma	Foot	DGD	26.5	+	−	−
14	M	84	Malignant melanoma	Foot	IID	18.7	+	−	−
15	F	64	Malignant melanoma	Foot	DGD	28.5	+	−	−
16	M	43	Squamous cell carcinoma	Foot	DGD	21.2	+	+	−
17	M	72	Malignant melanoma	Thigh	IID	22.7	+	−	−

DGD deep groin dissection, *IIL* ilio-inguinal dissection, *BMI* body mass index (kg/m^2), *ICG* indocyanine-green

Table 2 Clinical characteristics of patients and surgical procedure

Characteristics	Number of patients (total $n = 17$)	p value
Age (years)		0.581
≥70	10	
<70	7	
Sex		0.238
Male	8	
Female	9	
BMI (kg/m^2)		0.419
≥23	7	
<23	10	
Level of dissection		0.238
DGD	9	
IIL	8	
Intervention based on ICG fluorescence angiography		0.003
−	9	
+	8	

DGD deep groin dissection, *IIL* ilio-inguinal dissection, *BMI* body mass index (kg/m^2), *ICG* indocyanine-green

The range of measurements is up to 2 cm from the body surface, corresponding to approximately the level of the muscle fascia [14] (2) To evaluate flap fluorescence, surgeons do not need to turn off all of the lights in the operating room (again, unlike fluorescein). (3) It is also unnecessary for surgeons to wear goggles that provide protection from ultraviolet light exposure when using ICG fluorescence. (4) The incidence of adverse reactions to ICG after intravenous or intraarterial injection is very low (0.17 %) [15]. The overall rate of adverse reactions after fluorescein angiography was 0.6 % for angiographic procedures [16]. In addition, Buchanan et al. [17] reported their experience with intravenous fluorescein that involved 38 administrations in 29 patients. In all, there was a drop in blood pressure of 20 mmHg or more in 24 % of patients, and the blood pressure fell by 60 mmHg or more in 8 % of the cases.

This surgical intervention using ICG fluorescence angiography is also useful in cases in which a thin skin flap must be elevated to remove a tumor or metastatic lymph node under the skin flap. In cases with anal or intrapelvic malignancies with metastatic swelling lymph nodes, surgeons have to elevate a thin skin flap to perform dissection of the groin lymph basin. The use of similar dissection-related procedures may be indicated for other malignancies.

Conclusion

Our surgical intervention based on ICG fluorescence angiography is potentially associated with a decreased risk of

postoperative wound dehiscence after ILND. This procedure is safer and easier to perform than fluorescein angiography. The routine use of ICG fluorescence angiography is therefore recommended for Stage III skin cancer patients with a high risk of wound complications after ILND.

Conflict of interest H. Furukawa and co-authors have no conflicts of interest to declare in association with this study.

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