Lymphedema secondary to melanoma treatments: diagnosis, evaluation, and treatments

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Abstract: Approximately 300,000 new cases of melanoma are annually diagnosed in the world. Advanced stage melanomas require sentinel lymph node biopsy (SLNB), sometimes lymph node dissections (LND). The development rate of lower extremity lymphedema ranges from 7.6% to 35.1% after inguinal SLNB, and from 48.8% to 82.5% after inguinal LND. Development rate of upper extremity lymphedema ranges from 4.4% to 14.6% after axillary LND. Lymphedema management has constantly improved but effective evaluation and surgical management such as supermicrosurgical lymphaticovenular anastomosis (LVA) are becoming common as minimally invasive lymphatic surgery. Diagnosis and new classification using indocyanine green lymphography allowing pre-clinical secondary lymphedema stage management are improving effectiveness of supermicrosurgical LVA and vascularized lymph node transfer. Lymphatic transfer with lymph-interpositional-flap can restore lymph flow after large oncologic excision even without performing lymphatic anastomosis. Since lymphatic reconstructive surgery may affect local to systemic dissemination of remnant tumor cells, careful consideration is required to evaluate indication of surgical treatments.

Keywords: lymphedema, melanoma, anastomosis, lymph node, supermicrosurgery

Introduction

Melanoma is an aggressive cutaneous cancer affecting 287,723 new patients and responsible for 60,712 deaths in 2018 in the world (1). Existence of metastatic regional lymph nodes is one of the most impairing factors on staging and survival prognosis (2,3). Sentinel lymph node biopsy (SLNB) is the standard procedure to determine the lymph node metastatic status and, according to the American and European recommendations, complete lymph node dissection (CLND) should be done if the sentinel lymph node is positive (4,5).

Despite these recommendations, this procedure is debated due to the morbidity of CLND and the limited oncologic benefit for some patients, but these conclusions are limited by inclusions bias (6-10). The SLNB and CLND morbidities are highly attributable to secondary lymphedema and its consequences such as chronic limb swelling responsible for discomfort and functional impairment, recurrent bacterial and fungal infection, ulcerations, psychosocial and cosmetic impairments (11). Also, several modifications of surgical technique have been suggested to reduce risk of complications, including preservation of the saphenous vein (12,13).

Despite these surgical improvements, lymph node dissections for melanoma treatment still lead to rates between 15.7% and 64.3% of secondary lymphedema (14-18). The purpose of this article is to focus on characteristics of secondary lymphedema after melanoma treatment and to report state-of-the-art secondary lymphedema treatments.

Extremity Lymphedema (EL) in melanoma

Lower extremity lymphedema (LEL)

European and American guidelines recommend regional lymph nodes dissection in the treatment of melanoma with positive sentinel lymph node (4,5). In the lower limb, the recommended lymphadenectomy is the femoro-inguinal lymph node dissection. SLNB is the standard procedure to determine lymph node metastatic status.

Lower extremity lymphedema (LEL) is the one of the most frequent complication of both SLNB and inguinal lymph node dissection (ILND) in melanoma. Reported rates of LEL secondary to inguinal SLNB were from 7.6% to 35.1% and from 48.8% to 82.5% after ILND (16,19). These rates are higher than the LEL rates reported after surgical treatment of advanced...
pelvic cancers. According to studies, the LEL rate range after pelvic cancer is between 36.9% and 61% (20-24).

NEL in melanoma has a different physiopathology of the NEL secondary to lymphadenectomy for pelvic cancer, which is the cause of a higher rate of NEL. Indeed, American and European guidelines recommend pelvic lymphadenectomy and para-aortic lymphadenectomy in advanced gynecological and prostatic cancer (25-31). However, these lymphadenectomies preserve the superficial limb lymph nodes that are removed during the ILND for melanoma. Pelvic and para-aortic lymph node dissection are indirectly responsible for the obstruction of the lower limb superficial lymph flow whereas ILND for melanoma are directly responsible for it. The difference of NEL rates between melanoma and pelvic cancer seems to be due to the difference of lymph node dissection. The wide local excision seems to not be implicated in NEL, no study reported NEL after melanoma excision (14-16,32). However, no study compared lymph circulation patterns before and after local wide excision.

**Upper extremity lymphedema (UEL)**

Axillary lymph node dissection (ALND) is recommended for treatment for both advanced breast cancer and melanoma. The upper extremity lymphedema (UEL) rates after ALND were from 4.4% to 14.6% in the reported studies and from 4.1% to 21.4% after ALND for breast cancer (16-19,33-37). These two rates are similar probably because the ALND is the same for both cancers. ALND directly affects the upper limb superficial lymph flows. Also, no study compared lyphatic pattern before and after excision but the fact that these rates are similar is possibly due to the non-implication of wide local excision melanoma in UEL.

**Diagnosis**

**Clinical manifestation of lymphedema**

A heaviness sensation of the limb is the first manifestation of extremity lymphedema (EL). Extremity discomfort, tension, pain or tingling sensations can also be felt mostly during the evening. Edema can affect one, two or three limb parts depending on the EL stage. Other causes of edema such as heart failure, hepatic failure, nephrotic syndrome, cancer and venous insufficiency have to be excluded. In severe cases, EL can be associated with acute skin infections such as cellulitis and chronic inflammation causing skin thickening, interstitial tissue fibrosis, hyperkeratosis, and/or chronic ulcerations.

The International Society of Lymphology classification is based on physical condition of the extremities (38). Stage 0 refers to a latent or subclinical lymphedema without swelling. Stage I represents an early accumulation of fluid relatively high in protein content which subsides with limb elevation. Stage II signifies that limb elevation alone rarely reduces the tissue swelling and pitting is manifested except in late stage II when fibrosis is developed. Stage III encompasses lymphostatic elephantiasis where pitting can be absent and trophic skin changes are seen.

**Imaging**

Complementary imaging examinations in both primary and secondary lymphedema are fundamental. They help to confirm the diagnosis by showing involvement of a pathologic lymphatic system in edema, they allow to stage lymphedema and to schedule surgical procedures.

**Indocyanine green (ICG) lymphography**

ICG lymphography is used to study the superficial lymphatic system. Using a near infrared fluorescence camera, subcutaneously or intradermally injected ICG shows enhancement of fluorescent image of superficial lymph circulation up to 2 cm from the skin surface in real time. More related to the pathogenic mechanism of lymphedema, ICG lymphography severity staging has been developed based on the anatomy and the functional superficial lymphatic vessels as seen in ICG lymphography (Table 1) (39). Four patterns of ICG lymphography findings are correlated with clinical stage. Linear pattern (Figure 1A) is related to normally functional superficial lymphatic collectors. When lymph flows are obstructed, the lymphatic collectors become dilated, leading to retrograde lymph flows called dermal backflow.

The first and less severe dermal backflow pattern is the splash pattern (Figure 1B) that is correlated with lymphatic reflux into the more superficial collecting and precollecting lymphatic vessels, showing tortuous lines on ICG lymphography. The second dermal backflow pattern is the stardust pattern (Figure 1C) correlated with precollecting lymphatic vessels, showing tortuous and dilated lymph vessels. The third pattern is the stardust pattern with hyperemia, which is correlated with lymphatic vessels that are out of functional deep collecting lymphatic collectors (Figure 1D) (228).

| Table 1. Pathophysiological severity stage based on ICG lymphography findings |
|-------------------------------|------------------|------------------|
| ICG stage | Lymphography findings | Clinical conditions |
| stage 0 | Linear pattern only (no DB pattern) | No lymphedema |
| stage I | Splash pattern (+ Linear pattern) | Subclinical lymphedema |
| stage II | SD pattern in 1 region (+ Linear pattern) | Early lymphedema |
| stage III | SD pattern in 2 region (+ Linear pattern) | Progressed lymphedema |
| stage IV | SD pattern in 3 region (+ Linear pattern) | |
| stage V | SD pattern only (no Linear pattern) | |

Upper/lower extremity can be divided into 3 regions; the upper-arm/thigh, the forearm/lower-leg, and the hand/foot. ICG, indocyanine green; DB, dermal backflow; SD, Stardust and/or Diffuse.
localization and function of the collateral network. Contrast diffusion can, as in ICG lymphography, reveal dermal backflow. However, injections are required and, recurrent irradiation in post-cancer patients should be limited. Moreover, regarding lymphatic disease progression or post-surgical evolution and their availability, some centers cannot afford to repeat these examinations.

**Lymphedema management**

**Non-surgical Management**

**Medical management**

No medical treatment is indicated in routine management of lymphedema however, some studies reported an effect of medical treatment on EL. Results of studies focusing on coumarin, diosmin and arbutin are contrasted and, due to hepatotoxicity, there is no recommendation for routine use \(^{47,48}\). Diuretics are considered a contraindication. Antibiotics are recommended to prevent recurrence of limb cellulitis but are not effective for lymphedema. The overuse of antibiotics increases the risk of emergence of multi-drug resistant bacterial infection.

**Decongestive therapy**

Physiotherapeutic management of EL has been reported to be effective. Studies proved that pneumatic compression are effective on EL \(^{49-52}\). Treatment of lymphedema with complete decongestive physiotherapy (CDT), which combines manual lymphatic drainage, lymphedema rehabilitation exercises, compression therapy, and skin care, can achieve a 45-70% reduction in EL volume \(^{48-50}\). Phase 1 of CDT consists of skin care and manual lymphatic drainage. Phase 2 consists of compression, manual drainage and exercises to conserve the benefit obtained in phase 1.

Magnetotherapy and electrotherapy have also shown good results \(^{53}\). Intermittent pneumatic compression has shown good results but only a few studies have been published. It is understood that compression therapy used in CDT is effective in EL treatment but has to be adapted so as not to reduce the quality of life \(^{54-56}\). Thermal therapy, aquatherapy, low-level laser therapy and ultrasounds therapy have also been suggested.

All of this non-surgical management is anti-symptomatic treatment and not curative, because it cannot restore lymph flow. Therefore, life-long treatment is required.

**Surgical management**

EL surgical treatment includes several procedures which can be separated into two groups: physiological and ablative surgeries. Physiological surgeries aim to restore lymph drainage to the lymphatic system, venous system or new lymphatic pathways after lymphangiogenesis.
whereas ablative surgeries remove affected tissues (36, 57–59). Physiological surgeries are so classified:

- Lymphatic bypasses which aim to divert congested lymph to intact lymphatic or venous circulation. They can be classified into lymphatico-lymphatic bypass, lymphatico-venous implantation, lymph node to vein shunt and lymphaticovenular anastomosis.
- Lymphatic transfers from a healthy lymphatic donor site. They include vascularized lymph node transfer with or without efferent lymphatic vessel anastomosis, and lymph-interpositional-flap transfer (LIFT).

**Lymphatic bypass**

**Lymphatico-lymphatic bypass**: Lymphatic to lymphatic bypass, using a lymphatic graft seems more physiologic. It has been reported on a 329 patient series that more than 60% of the patients with UEL showed a reduction in volume difference to the healthy side of more than 50% after a mean follow-up period of more than 2 years (60). However, this technique is invasive for the donor site with a risk of lymphedema on the donor site.

**Lymph node to vein anastomosis and lymph node implantation**: The implantation uses microsurgical techniques to insert lymphatic vessels into a vein. Some authors reported good results but the thrombosis risk is higher than in supermicrosurgical lymphaticovenular anastomosis (LVA) because the lymphatic vessel adventitia is in contact with the venous lumen (61-63). Serious complications such as deep venous thrombosis and pulmonary embolism were reported. Because of high risk of thrombosis and possibility of serious sequelae, this procedure has been abandoned by most lymphatic surgeons.

**Supermicrosurgical lymphaticovenular anastomosis (LVA)**: Unlike the above mentioned classical lymphovenous shunt operations, supermicrosurgical LVA creates a real anastomosis of lymphatic vessel to recipient venule or small vein in an intima-to-intima coaptation manner. Since lymphatic vessels can be smaller than 0.5 mm, supermicrosurgical techniques which allow anastomosis of vessels with an external diameter of 0.5 mm or smaller, is necessary to perform LVA surgery. LVA are an anastomosis between a superficial lymphatic vessel (mostly under the superficial fascia) and a superficial vein. Supermicrosurgical anastomosis allows intima-to-intima coaptation even when vessel diameters are smaller than 0.5 mm.

LVA is performed in an end-to-end, side-to-end, side-to-side, or end-to-side fashion. Various anastomotic configurations can be combined to maximize lymph flow drainage. Lambda-shaped LVA allows bidirectional bypass using a lymphatic vessel and a vein with end-to-end and end-to-side anastomosis (64-72). LVA is the least invasive surgery to treat lymphedema. It can be performed under local anesthesia through an approximately 2 cm incision allowing for day surgery.

**Lymphatic transfer**

**Vascularized lymph node transfer (VLNT)**: VLNT is a reconstructive lymphatic surgery mainly for advanced cases where lumen of lymphatic vessels are obstructed because of lymphosclerosis or patients where lymphatic vessels are not found. VLNT requires less technically demanding procedures, since supermicrosurgery is not basically needed (73, 74). Supemicrosurgery is required, when the efferent lymphatic vessel of a transferred lymph node is anastomosed (58).

Two different mechanisms are suggested to explain VLNT effects. The first one is that VLNT would act like a bridge over the obstruction zone because the VLNT flap contains many functional lymphatic vessels and nodes. Therefore, the VLNT flap has to be large enough to reach both beyond the obstruction, and to reconnect lymphatics on both sides via lymphangiogenesis (74). The other mechanism is that the VLNT flap would act like a lymphatic pump to the blood circulation (75).

Several donor sites have been identified; inguinal, lateral thoracic, supraclavicular submental and omentum. On a literature review of about 271 VLNT cases (24 studies), Scaglioni et al. reported that submental VLNT were the most effective with 100% of patients showing improvement, the supraclavicular was the second highest rate of benefit (88.2%), followed by the inguinal VLNT (70.4%, n = 138), 60% of omental VLNT demonstrated benefit, and only 5% of lateral thoracic VLNT reported an improvement. The highest complication rate on donor site was on lateral thoracic (15.8%), then in inguinal (10.9%), supraclavicular (1.2%) and submental (0%) and omentum (0%). Donor site lymphedema was more frequent in lateral thoracic (13.2%) and inguinal (1.6%). No donor site lymphedema was reported on supraclavicular, submental or omentum.

**Lymph-interpositional-flap transfer (LIFT)**: Traumatic lesions and oncologic excisions can interrupt lymphatic flow and lead to lymphedema. A retrospective study suggested that tissue replantation or reconstruction could restore lymph flow without lymph node transfer or lymphatic vessel anastomosis (59). This study showed that spontaneous lymph flow restoration depended on compatible lymph axiality without raw surface in lymph axiality. When lymphatic vessel stumps in a recipient site and transferred tissue were approximated to each other, the lymphatic vessels could be reconnected spontaneously without supermicrosurgical lymphatic anastomosis. Based on the concept of lymph axiality, a new lymphatic reconstruction, LIFT, has been developed, allowing lymph flow reconstruction without supermicrosurgical technique or lymph node sacrifice. Since LIFT does not sacrifice lymph nodes at the donor site, donor site lymphedema risk is significantly reduced unlike VLNT.

For LIFT operation, ICG lymphography is necessary to precisely localize lymphatic vessels both in a donor flap and a recipient site. Linear patterns from flaps were
aligned as best possible to the donor site linear patterns under ICG lymphography surgical navigation. LIFT can be applied for primary prevention of lymphedema in oncological ablative surgery and for treatment of established secondary lymphedema.

**Debulking surgeries: resection and liposuction**

Chronic lymphedema is responsible for damaging soft tissues and leads to a dermato-lipofibrosclerosis. Patients with severe stage lymphedema can be affected by recurrent fungal and bacteriologic infections, as well as elephantiasis and have a deformed extremity limiting compression effectiveness. Once fat deposition and fibrotic histopathological changes occur, reconstructive surgery cannot improve the changes, and some debulking procedures may be required to improve the established histopathologic changes. Unlike lymphatic reconstructive surgery, debulking surgeries aim to decrease lymphedematous volume directly by removing the lymphedematous tissue, allowing without an immediate affect of volume reduction. However, debulking procedures destroy the remaining lymphatic structures, and worsen lymph circulation. Therefore, even stronger compression treatment is required after some debulking surgeries.

Charles’ procedure was a surgical excision management described in 1912. The treated limb part (thigh or thigh+leg) is circumferentially denuded down to the deep fascia. The deep fascia thickness is also reduced to a normal size. The excised tissue is used as a donor site for split thickness skin graft. Feins described a Hofman’s procedure. Skin incision is done from up to down in the affected limb. Two skin flaps are harvested. Lymphedematous tissues from subcutaneous fat to deep fascia are excised. After hemostasis, skin flaps are replaced on muscles. Depending on volume excess, this procedure can be repeated (76). Some authors describe improvement of clinical conditions and quality of life after excisional surgery or liposuction on severe lymphedematous patients (77,78). This type of surgery should be considered only after failure of all physiologic treatments and only when patient’s compliance for maximum compression therapy is confirmed, because lymphedematous tissues shall re-increase as lymph circulation is even further deteriorated after debulking procedures; debulking procedures can also be destructive to remaining lymphatic functions.

**Conclusion**

Secondary limb lymphedema after SLNB or CLND for melanoma affects a high percentage of patients and lymphatic follow-up should systematically be considered. Lymphatic surgeries after melanoma may present a possible risk to accelerate dissemination of a local melanoma recurrence, which should be well evaluated before performing lymphatic surgeries.

**References**


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