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Management of Acral Lentiginous Melanoma

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/54266>

1. Introduction

Cutaneous malignant melanoma is the most common cause of mortality from skin cancers in Caucasian populations. The incidence rates of malignant melanoma show considerable variation worldwide. Annual incidence rates per 100,000 people vary between about 40 in Australia and New Zealand to about 20 in the United States [1,2]. In contrast, a significantly lower incidence rate has been reported in Asian populations with rates of 0.65 to 1/100,000 [3-5]. In addition, the most common sites of melanoma occurrence in Asians are the extremities at a rate of about 50% of all cases [6,7], compared to only 2-3% in Caucasian populations [8].

In 1976, RJ Reed first described the fourth variant of melanoma as “pigmented lesions on the extremities, particularly on palmoplantar regions, that are characterized by a lentiginous (radial) growth phase evolving over months or years to a dermal (vertical) invasive stage” [9]. He named this anatomical subgroup of melanoma as “plantar lentiginous melanoma (PLM)”, which had a characteristic lentiginous, radial component of melanocytic proliferation and mentioned for the first time that this subgroup was the most common in Blacks and the very poor prognosis group [10].

In 1986, malignant melanoma was classified into four subtypes by Clark et al. according to histological features; nodular melanoma (NM), superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM) [11]. In the United States, the incidence rates of SSM, NM, LMM and ALM are approximately 70%, 15%, 13% and 2-3% respectively [12,13]. Although, ALM is the most common expression of malignant melanoma in Asian and Black populations, the rate of ALM is 41% in Japan [14], 65% in Korea [15] and 62% in the American Blacks [16].

The prognosis of each subtype differs due to delayed diagnosis rather than an actual differences in the biological nature of tumour and the prognosis of ALM is generally poorer than other subtypes [17]. The lesion, especially on soles and nail beds, is likely to be overlooked by pa-

tients. Moreover, Metzger et al. found that ALM had a high likelihood of being clinically misdiagnosed as a benign melanocytic lesion, which leads to a delay in the initiation of treatment [18]. However, this report was made in the pre-dermoscopic era and now it has become much easier with dermoscopy to distinguish the early stage of ALM from a benign lesion.

Human extremities, especially palms and soles, are not exposed to ultraviolet light and there is no evidence of overexposure to UV light as a risk factor of ALM [19]. In contrast, UV light plays an important role in the pathogenesis of LMM.

In 2005, Bastian et al. proposed new classification of melanoma according to genetic alterations at different sites. They classified melanoma into four distinct groups, each of which has a different degree of exposure to UV light: chronic sun-damaged melanoma (CSD) which nearly corresponds to LMM, non-CSD melanoma which also corresponds to SSM, acral melanoma (AM) which also corresponds to ALM, and mucosal melanoma [20]. They found that 81% of non-CSD melanoma had mutations in BRAF or N-RAS and the other groups had no mutations in either gene. Otherwise, melanoma with wild-type BRAF or N-RAS frequently had an increase in the number of copies of the genes for cyclin-dependent kinase 4 (CDK4) and cyclin D1 (CCND1). Furthermore, a recent study showed that AM and mucosal melanoma had frequent mutation or amplification of the KIT gene [21]. Although these findings have led to molecular targeted therapy today, this new therapeutic approach has just begun and therefore we will only touch upon these new directions.

Today, there are some difficulties and controversies in the treatment of ALM caused by the anatomical and biological specificity of ALM. The standardized treatment of ALM is not easy to establish due to the unique characteristics. This chapter includes our experiences and a review of the literature focusing on the surgical treatment of ALM, and in particular, discusses the controversies surrounding the treatment of ALM.

Clinical presentation and dermoscopic findings of ALM

ALM occurs more frequently on lower extremities than on upper extremities. In our institute, 41 cases of all 61 ALM cases occurred on lower extremities. The soles of the feet are the most frequent sites of ALM, where 56% of ALM on lower extremities occurred. In contrast, most frequent sites on upper extremities are fingernails, where 45% of ALM on upper extremities appeared.

Clinically, ALMs begin with pale brown macules, enlarge slowly and form irregularly pigmented, asymmetric macular lesions with notching at the periphery over the years. After that, nodules appear on the pigmented lesion and form ulceration. In the past ALM was considered to occur from benign melanocytic lesions, however, de novo synthesis in major cases of ALM has been confirmed by dermoscopic findings (see below). Due to the very slow progress, it tends to be overlooked and even when the tumour becomes larger, it is easily underestimated.

Histologically, “(1) the radial growth phase consists of lentiginous dysplastic melanocytes, extending along the basal cell layer, with extension of single atypical melanocytes up into the thickened epidermis; (2) the vertical growth phase usually consists of a progressive cen-

tral plaque-like thickening of malignant cells in the papillary dermis, with (3) extension of the spindle cells into the deeper levels, accompanied by prominent dysplasia; (4) there is epidermal hyperplasia with elongation of the rete ridges and acanthosis and central ulceration; and (5) host immune response is active, with areas of tumor regression” [22].

	Location	Case Number (%)
Lower extremities	Thigh	1 (1.6)
	Lower leg	6 (9.8)
	Dorsum of foot	1 (1.6)
	Sole	23 (37.7)
	Toe	8 (13.1)
	Toenail	2 (3.3)
	Total	41
Upper extremities	Upper arm	0 (0)
	Forearm	1 (1.6)
	Dorsum of Hand	1 (1.6)
	Palm	4 (6.6)
	Finger	4 (6.6)
	Fingernail	9 (14.8)
	Total	19
Unknown		1 (1.6)
Total		61 (100)

Table 1. Primary sites of cutaneous melanoma experienced in our institute from 2004 to 2011

Dermoscopic observations help the diagnosis in the early stage of ALM. In 66 cases of volar skin melanomas, irregular diffuse pigmentation (60%) with variable shades from tan to black without parallel disposition of pigment (figure 1a) and the parallel ridge pattern (53%) with pigmentation along the ridges (figure 1b) were the two most prevalent patterns [23]. According to Saida et al., the sensitivity and specificity of the parallel ridge pattern in diagnosing all melanoma on volar skins were 86% and 99% respectively and those of irregular diffuse pigmentation were 85% and 97% respectively. Only in diagnosing melanoma in situ on volar skin, the sensitivity of parallel ridge pattern (86%) was significantly higher than that of irregular diffuse pigmentation (69%) [24]. A parallel furrow pattern with pigmentation along the furrows (figure 1c) and a lattice-like pattern with longitudinal and transversal thicker lines surrounding the eccrine pores (figure 1d) are more common in melanocytic nevi. The sensitivity and specificity of a parallel furrow pattern or lattice-like pattern in diagnosing melanocytic nevi were 67% and 93% respectively [24].

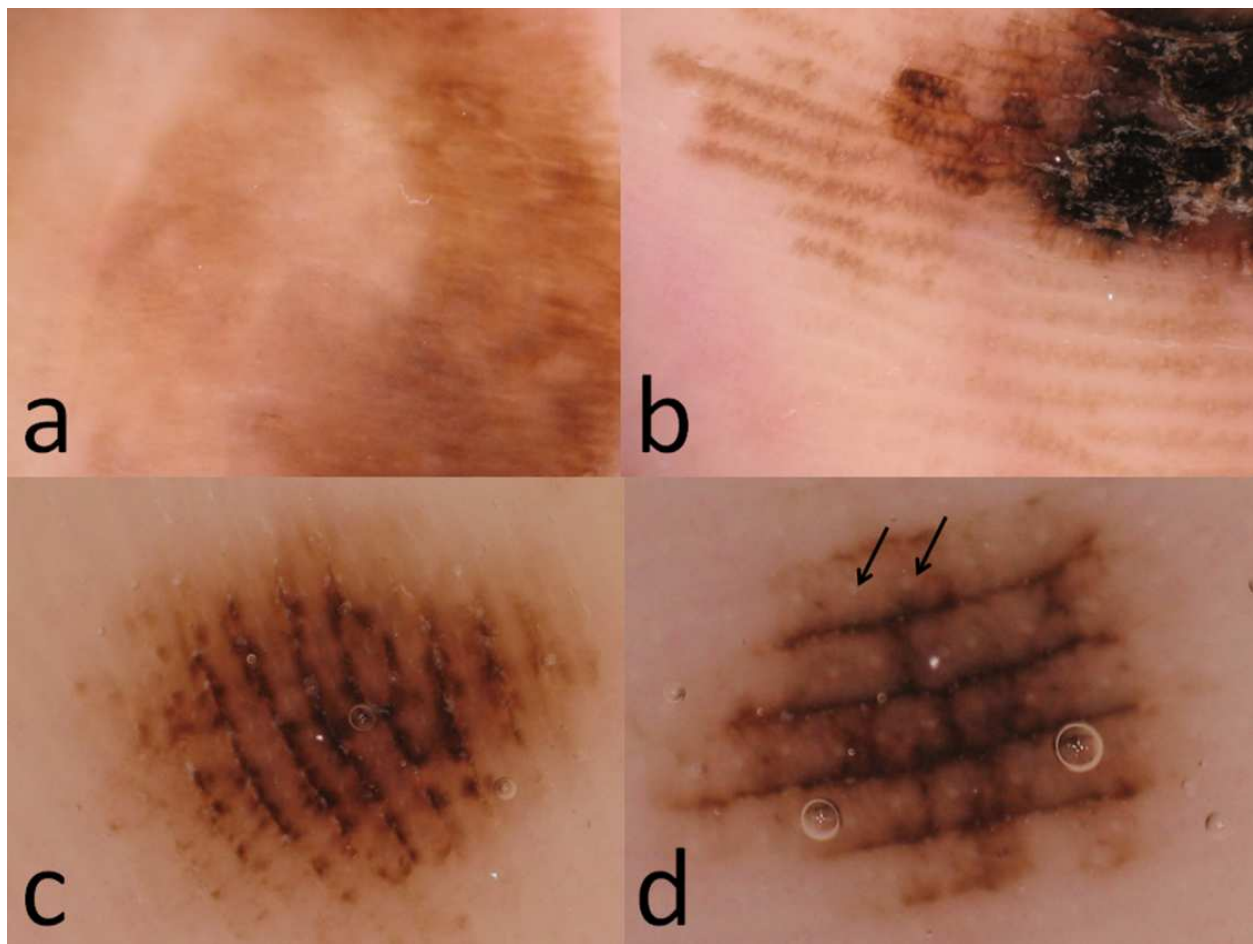


Figure 1. Dermoscopy of early stage ALM (a,b) and melanocytic nevi (c,d). (a) Irregular diffuse pigmentation, (b) parallel ridge pattern, (c) parallel furrow pattern, (d) lattice-like pattern with longitudinal and transversal thicker lines surrounding the eccrine pores (arrows).

Ulceration on nodules following pigmented macules reveals a polymorphous vascular pattern with a combination of milky-red areas (95%) which are larger areas of fuzzy or unfocused milky-red colour corresponding to an elevated part of the lesion, linear irregular vessels (49%), dotted vessels (43%) and hairpin vessels (41%) [25].

2. Subungual melanoma

The incidence of subungual melanoma also has a racial difference. It is more frequent in Asian and Blacks than in Caucasians. Its frequency has been reported to be approximately 2-4% in all cutaneous melanomas in Caucasians and 10% in Japanese [26]. Of the 108 subungual melanomas in Japan, the cases involving fingers and toes were 76% and 24% respectively. On both fingers and toes, the thumb and the great toe were the most common sites [26]. Among the subungual melanoma, the occurrence rate of ALM on the fingernail is higher than on toenails. According to the literature, of 64 cases of subungual melanoma, 55% cas-

es occurred on the thumbnail, 27% on the nail of the great toe, 2-4% on the nail of the index, middle and ring finger, 1.6% on the nail of the second toe [27].

It is known that subungual melanoma has a very poor prognosis among all subtypes of cutaneous melanomas. The reason for this is because the majority of subungual melanomas are already been quite deep when diagnosed [28]. Delayed diagnosis of subungual melanoma is common because it is very difficult to distinguish the early stage of subungual melanoma from longitudinal melanonychia. According to Cohen et al., 38 of 43 patients (88%) had delayed diagnosis and the median delay time was 24 months (range 4 to 132) [29].

Subungual melanomas begin with fine pigmented striata which could not be clinically distinguished from benign longitudinal melanonychia at an early stage and grow wider with colour variegation and the presence of nail plate fissuring or splitting eventually forming a triangular shape which has a broader proximal lesion rather than a distal lesion, blurred lateral borders and Hutchinson's sign - indicating the peripheral pigmentation beyond the nail apparatus [30].

Baran et al. mentioned the clinical clues to the diagnosis of subungual melanoma in detail. Hutchinson's sign is the most important sign of subungual melanoma. Other clues are when longitudinal melanonychia (a) begins in a single digit of a person over six decades or more, (b) develops abruptly in a previous normal nail plate, (c) becomes suddenly darker or wider, (d) occurs in either the thumb, index finger or giant toe, (e) is accompanied by nail destruction or disappearance, (f) has colour variegation, (g) has a wide band and so on [31].

In addition to these clinical clues, dermoscopy provides useful information for the diagnosis of subungual melanoma. The prominent dermoscopic features of subungual melanoma are brown pigmentation of the background with longitudinal brown to black lines which are irregular in their colouration, spacing, thickness and parallelism [32]. This irregularity was significantly associated with melanoma when compared with all other benign diseases. The micro-Hutchinson's sign is the suspicious dermoscopic feature, which consists of the irregular lines in the cuticle area and can be observed only on dermoscopy [32,33].

Since the early stage of subungual melanoma has minimal histopathological change, it may be difficult to distinguish subungual melanoma from benign lesion with only histopathological findings. Thus, both clinical features, including present history and histopathological findings, are necessary for diagnosis.

We propose a diagnostic algorithm for the early stage of subungual melanoma (figure 2). When a case falls under any of the clinical features mentioned above (a-g), dermoscopic examination is recommended. If Hutchinson's sign and colour change in overall nail to dark black are present, excisional biopsy is recommended. When those characteristic appearances are absent, but a nail streak has irregularity, biopsy is also recommended. On the contrary, when nail streaks are monotonous pale brown, subungual melanoma is not suspicious. Even if a streak is dark brown or black, no irregularity of lines on dermoscopy allows careful follow-up without biopsies. If the streak increases in width or has colour variegation during a period of follow-up, the necessity of excision or biopsy should be discussed according to further dermoscopic examination.

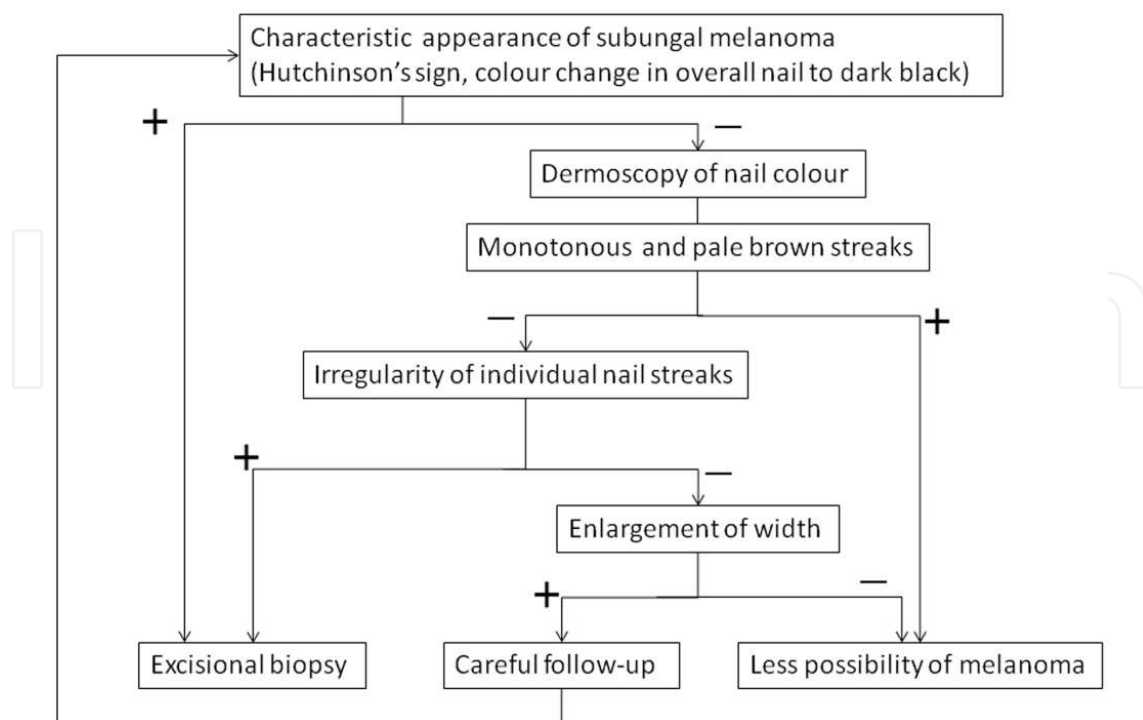


Figure 2. Diagnostic algorithm for early stage subungual melanoma.

Since nail biopsies cause cosmetic problems, biopsy methods should be selected as follows. If streaks are more likely to be melanoma, complete excisional biopsies are desirable. If it is less likely, punch biopsies around the origin of the longitudinal melanonychia (which is frequently located on the nail matrix) can be chosen. When excisional biopsies are performed, we should keep in mind that an insufficient margin at the proximal side of the nail may cause incision in between the lesional nail matrix without including the whole lesion. Ultra-sound echography provides useful information on the location of the nail matrix [34], so that a sufficient margin can be ensured. Furthermore, it is desirable that extent of the excisional biopsy includes the periosteum of the distal phalanx. Since the distance between the nail matrix and bone is extremely close at the proximal side, excisional biopsies excluding periosteum may incise the nail matrix and leave some lesion on the body. Excisional biopsies including the periosteum causes very little disadvantage compared with those excluding the periosteum and afterwards good granulation tissue will be formed on the bone when the artificial dermis is used. If it is histopathologically diagnosed as subungual melanoma, a local wide excision is selected, excluding the case when a sufficient margin is ensured at the previous excisional biopsy.

Excisional biopsies in a good manner allow us to determine correct tumour thickness, which provides important information on the choice of SLNB, local wide excision and chemotherapy. However, biopsy specimens easily break down if the biopsy procedure for histological examination is not performed well, which may cause incorrect choices for treatment.

If nail destruction is present under diagnosis of subungual melanoma, amputation of the distal phalanx will be applied on the assumption that the lesion invades the periosteum or

bone. However, not all cases of nail destruction are accompanied with invasion. Some cases of nail destruction may be melanomas in situ. Since the distance between nail bed and bone is wider at the distal side than at the proximal side, the possibility of avoiding amputation is higher when the nail destruction is modest and located at the distal side of the nail.

Moehrle et al. proposed 'functional' surgery for subungual melanoma, by which the amputation of the distal phalanx could be avoided and the more digital function could be preserved [35]. The tumour was surgically removed with measurable excision margins and a partial resection of the distal part of the distal phalanx was performed with a Luer instrument. After the resection, three-dimensional histology was performed as described in the literature [36]. Two of 31 patients had local recurrence after this operation. This method did not lead to shorter survival when compared to amputation, thus, it is worth considering.

3. Wide local excision

According to a review of the literature on the margins of radical excision for melanomas thinner than 2mm, the French Cooperative Group Trial [37] and the Scandinavian Melanoma Group Study [38] compared 2cm with 5cm margins and the World Health Organization (WHO) Melanoma Program Trial 10 [39] compared 1cm with 3cm margins. All three trials demonstrated no benefits for wider margins.

Although a 5mm margin for melanoma in situ is frequently recommended in some national guidelines, Kunishige et al. demonstrated that 86% of 1120 melanomas in situ were successfully excised with a 6mm margin and 98.9% with a 9mm margin. They concluded that a 6mm margin for melanomas in situ was inadequate and a 9mm margin was necessary [40].

A 1cm margin of excision has been proposed for melanomas less than 1mm thick and a wider margin for more than 1mm thick [41,42]. Although many national guidelines recommend that a 1 cm margin is appropriate for 1-2mm thick invasive melanoma, this is less clear because there has been very little data indicating that a 1cm margin for 1-2mm thick melanoma is safer than 2cm margin [43]. For more than 2mm thick melanomas, a 2cm margin is considered to be sufficient in almost all cases. Depth of excision has been recommended to be at least the level of muscle fascia and deeper excision under it has not been shown to improve outcome [43-45].

For melanomas on the extremities, especially on fingers, amputation impairs the function. Thus, even if finger amputation is necessary, it is desirable that the defect is smaller so that functional impairment can be minimal. Detailed histopathological examination of resected specimens may allow surgeons to excise a smaller part of the fingers. We show the pathological specimen as illustrated on Figure 3. Because the resected margins are usually intricately curved, the specimen is divided into several parts so that a marginal side of each part becomes planar and paraffin sections can be made so that the whole surface of the marginal side can be examined. This technique provides highly accurate detection of continuous lesions with a small possibility of missing skip lesions. If the margin is negative, additional excision is not necessary and that provides preservation of more digital functions.

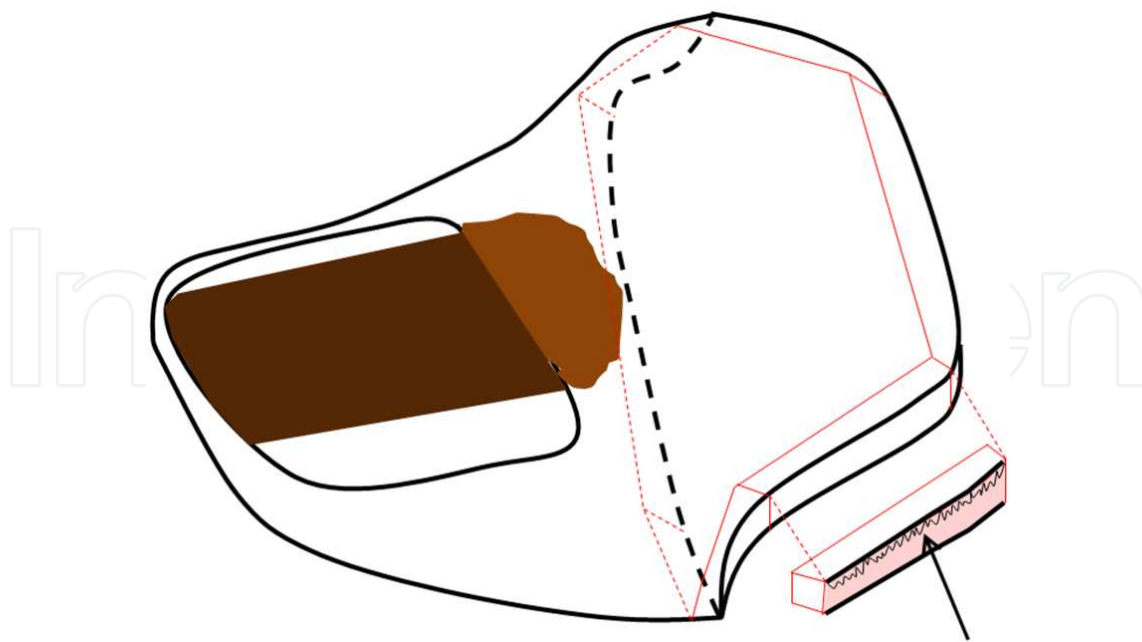


Figure 3. How to make pathological specimen of an amputated finger tip was illustrated. In order to examine the tumor cells at the marginal side accurately and continuously, curved rim of the excised margin was cut as linear as possible, and the outside of the margin is examined. (arrow)

4. Sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB) has become the standard procedure used to determine whether a tumour has metastasized to lymph nodes and more accurate staging of the melanoma. It is a less invasive technique than lymph node dissection allowing patients with node negative (N0) melanoma to avoid unnecessary lymph node dissection. In the case of SLN positive melanoma, additional surgery of lymph node dissection is necessary.

The false-negative rate in SLN mapping for melanoma has been reported to be very low with a rate of 0 to 2 % [46-49]. The multicenter selective lymphadenectomy trial-1 (MSLT-1) demonstrated immediate lymph node dissection following microscopic positive node at SLNB could bring about better prognosis than the lymph node dissection after clinical nodal observation [50].

For more correct mapping of SLNs, a combination of blue dye and radioisotope ^{99m}Tc labeled phytate is generally used. SLNs are identified by the presence of blue stained lymph vessels and lymph nodes, and the radioactivity measured by gamma probe. Furthermore, distinction between SLNs and secondary non-SLNs is achieved by using pre-operative dynamic cutaneous lymphoscintigraphy [51].

Although most melanomas drain to conventional regional nodes, unexpected drainage outside of these basins is observed in some cases. Pre-operative lymphoscintigraphy and a hand-held gamma probe are required for detection of these interval SLNs. According to a single-

institution study in Japan, SLNs were identified in 253 nodal basins from 117 patients and interval SLNs were found in six patients. They recognized 41 (17%) SLN metastases in 246 conventional nodal basins and one (14%) in seven interval SLNs [52].

5. Sentinel lymph node biopsy on upper extremities

Tumours on upper extremities almost always drain to the axillary region. The axillary region is divided into three parts based on the pectoralis minor. Level 1, 2 and 3 are located lateral, deep and medial to the pectoralis minor respectively. Outside this conventional region, SLNs are recognized in the cubital region and other areas. Figure 4 is the local sites of SLNs in our experience of 10 cases.

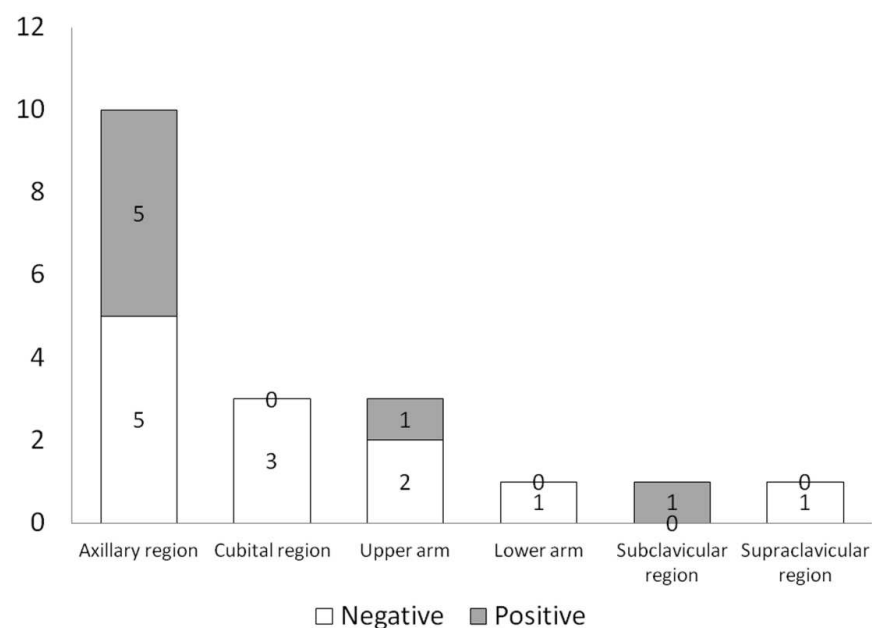


Figure 4. The sites of SLNs in primary melanomas on upper extremities.

SLNs were identified in all 10 cases (100%) for the axillary region, three cases (30%) for the cubital region, three cases (30%) for the upper arm, one case (10%) for the forearm, one case (10%) for the subclavicular region (level 3) and one case (10%) for the supraclavicular region. In all 10 cases, SLNs were present in anatomic level 1 of the axillary region. Although it has been considered that there is very little chance of finding SLNs in level 3, one case with SLN in level 3 was present in our data.

SLNs between the primary lesion and the axillary region are regarded as interval nodes on the upper extremities. Manganomi et al. reported that the interval SLN identification rate on upper extremities was 0.4% (two out of 480 cases) [53] and Kelly et al. reported 3.8% (16 out of 423 cases) [54]. Cubital region is the most common site of interval SLN on upper extremities. In our 3 cases of interval SLNs identified in cubital region, those were present on cubital

fossa and on ulnar side of cubital region. We have experienced five cases of other interval region rather than cubital region.

Tumours on upper extremities rarely drain to the subclavicular region (level 3) rather than to level 1 or 2. Our case with SLNs on the subclavicular region had positive with non-positive SLNs in level 11 and no SLNs in level 2 (Figure 5).

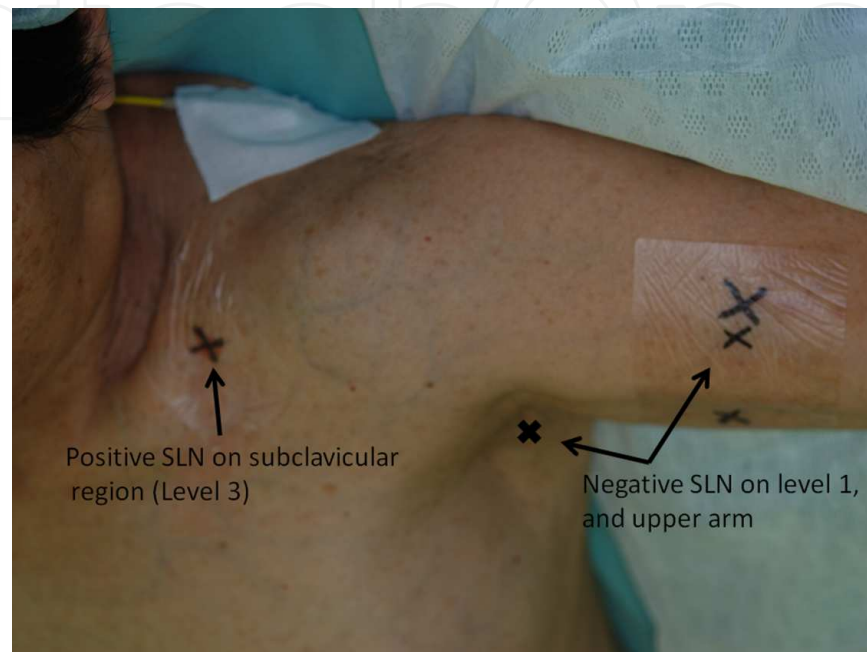


Figure 5. The case with positive SLN in level 3 and non-positive SLNs in level 1 and the upper arm. This metastatic pattern is extremely rare.

There may be cases where it is uncertain whether or not SLNB should be applied when tumour thickness is unknown. Some literature demonstrated that the patients with primary lesions on their extremities have a lower risk of misidentification of SLNs, even after wide local excision, than patients with axial primary lesions [55-59]. Tumors on central trunk may drain to both bilateral, or both axillary and inguinal regions. By contrast, tumours on extremities tend to drain more simply to the expected region. Although it is preferable that wide local excision and SLNB are performed at the same time, SLNB after wide local excision is less disruptive to lymphatic drainage in the case of primary lesions on the extremities than on axial sites.

6. Sentinel lymph node biopsy on lower extremities

In almost all cases, tumours on lower extremities drain to the inguinal region. Figure 6 demonstrates lymphatic drainage for 23 cases with tumours on lower extremities in our institute. Of all 23 cases, the lymph node identification rate was 23 cases (100%) for the inguinal region, five cases (21%) for the popliteal region and 10 cases (43%) for the pelvic region (nine

cases for external iliac lymph nodes and one case for the obturator region). Three of the 23 cases with SLN on the inguinal region had positive nodes and there were no positive nodes on the popliteal and pelvic region.

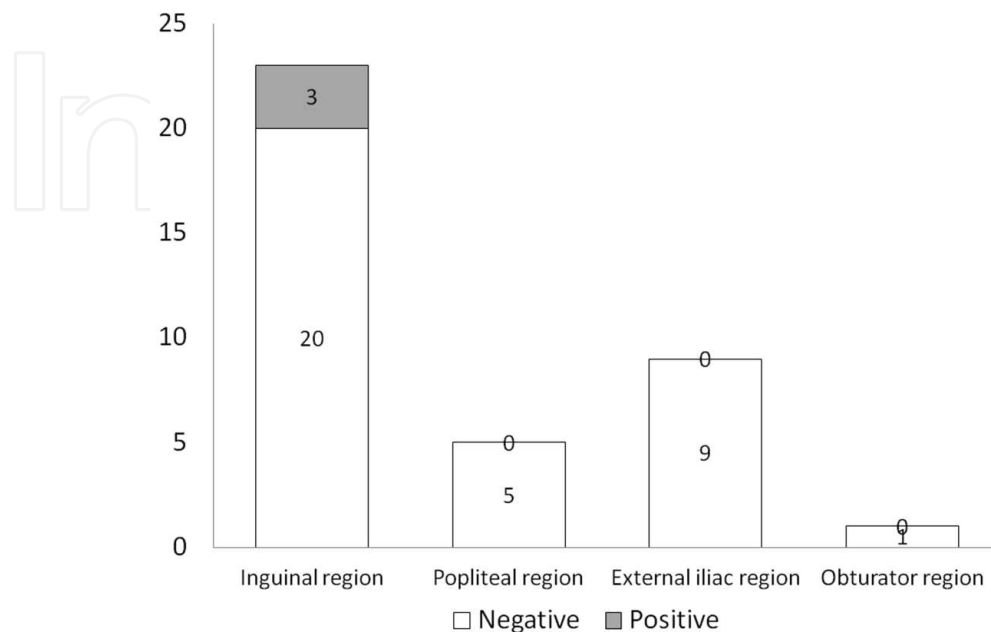


Figure 6. The sites of SLNs in primary melanomas on lower extremities.

One of the problems with SLNB of lower extremities is the presence of pelvic SLNs. Kaoutzanis et al. showed 11 of 82 cases with tumour on lower extremities had SLNs on the pelvic region and underwent SLNB [60]. They also showed that 19 of 82 cases (24%) had positive SLNs and all the positive SLNs were located in the inguinal region. No positive SLNs were present in the pelvic region as our cases.

Even in SLNB, removing the lymph nodes in the external iliac and obturator region is a relatively invasive technique. It is still controversial whether or not SLNs in the pelvic region should be harvested because SLNs in the pelvic region may be considered as secondary or third lymphatic basin, even when radioisotope is accumulated in pelvic lymph nodes.

Even now there is no consensus on the clinical definition of an SLN [61]. The SLN has been described as the hottest node, the blue node, first node visualized on lymphoscintigraphy and a node with radioactivity greater than twice or three times background radioactivity [61-63]. McMaster et al. recommended that all blue nodes and all nodes that measure 10% or higher of the 'ex vivo' radioactive count of hottest SLNs should be removed in order to decrease false-negative cases [64]. In our institute, SLN is defined as the node which showed higher than one tenth of the radioactivity of the hottest node. Because radioactivity depends on the distance from the surface of skin to the nodes, the measured radioactivity of the pelvic lymph nodes from the surface of skin is much less than superficial lymph nodes and tends to be underestimated [65]. Therefore, Bagaria et al. provided an answer that the back-

ground radioactivity of the regional nodal basin was measured before incision and all blue nodes and all hot nodes that have radioactivity greater than the background were harvested [61]. According to Soteldo et al., the rate of the cases that had metastasized lymph nodes in the pelvic region after SLNB that had indicated non-positive SLNs in the inguinal region was 2.4% [65]. This indicated that there might be cases with positive lymph nodes in the pelvic region with non-positive lymph nodes in the inguinal region. This rate should not be underestimated and gives a reason for removing SLNs in the pelvic region.

On the other hand, there have been no published results of positive pelvic lymph nodes with negative inguinal SLNs for melanoma located below the knee. Pelvic lymph nodes for melanoma located below the knee were considered as secondary lymphatic basin because they were not stained blue and the radioactivity of the pelvic lymph nodes was significantly less than that of the inguinal nodes removed from the same patients [66]. By contrast, the pelvic lymph nodes for melanoma located on the trunk and thigh are possibly SLNs. In the case of melanoma below the knee in which there is a risk or difficulty in removing the pelvic lymph nodes, for example the case of pelvic adhesion after surgery in the pelvis, SLNB could be clinically avoided in terms of the cost-benefit relationship.

There are two approaches to removing the pelvic lymph nodes. One is the technique with incision above the inguinal ligament and the other is the technique with median incision in the lower abdomen. Each technique has an advantage. With median incision, it is easier to approach a deep site in the pelvic region such as the obturator area or the external iliac region near to the common iliac region. By contrast, it is easier and less invasive to approach the external iliac region near to the inguinal ligament with an incision above the inguinal ligament.

7. Lymph node dissection

Lymph node dissection is the primary management for regional lymph node metastasis. It is applied in cases of clinical metastasis, positive SLNs after SLNB and histological lymphatic invasion for a resected or biopsied primary lesion. Surgical technique, extent of dissection, morbidity and complication vary widely in the published literature. Although lymph node dissection has been a standard treatment and the technique has not drastically changed for many years, even now there is much controversy surrounding lymph node dissection. Some of the controversies will be mentioned in the following section.

8. Axillary lymph node dissection

Since the tumours on upper extremities drain to the axillary region, axillary dissection is necessary and performed by way of cure or local control of the metastatic melanoma in the upper extremities. On the area of axillary dissection, it is controversial whether a level 3 dissection should be included. Namm et al. reported that the local recurrence rate of axillary

dissection including level 1 and 2 was 5 % (14 cases out of 270 cases) [67]. Guggenheim et al. also reported a rate of 4.5% after axillary dissection which mainly included level 1 and 2 [68]. On the other hand, according to Kretschmer et al., the local recurrence rate was 9.5% (six out of 63 cases) after dissection including level 1,2 and 3. There is no direct evidence that dissection including level 3 is superior to dissection without level 3 [69].

The complication rate of dissection for level 1 and 2 is less severe than that of dissection for level 1,2 and 3. The rates of infection and seroma after the former operation were 8% and 2% respectively, whereas those for the latter operation were 20% and 18% [67,70].

There are very few reported cases in which positive SLNs in level 3 were harvested except for our case. In addition, the lymph node ratio (LNR: the ratio of involved lymph nodes to total retrieved nodes in lymph node dissection) provides prognostic information [71-73]. There is very little possibility that positive lymph nodes are harvested only in level 3 without positive SLNs in level 1 or 2. Although there is data not on upper extremities but on lower extremities, a larger number of cases involved lymph nodes in the inguinal region with a higher rate of pelvic lymph node metastases [74]. This indicates that the number of superficial involved lymph nodes is related to the possibility of metastasis in the deep region. It has been reported that the size of SLN metastases predicts other nodal disease and survival in malignant melanoma [75,76]. Due to these findings, axillary dissection including level 3 is not always necessary when there are one or two micrometastatic lymph nodes in level 1, but it is necessary when a case falls under any of the following conditions:

- There is a relatively large clinically involved lymph node in level 1 or 2.
- There are many metastatic lymph nodes in level 1 or 2.
- There is negative SLNs in level 3 with positive lymph nodes in level 1 or 2.
- There are positive SLNs in level 3.
- There are involved lymph nodes in level 3 evaluated with radiological examination such as computed tomography (CT).

9. Inguinal and pelvic lymph node dissection

There is also controversy surrounding inguinal and pelvic lymph node dissection. The most controversial question is whether routine dissection with the primary tumour on lower extremities includes only a superficial inguinal lymph node dissection (SLND) or includes additional iliac and obturator lymph node dissection (deep pelvic/inguinal lymph node dissection : DLND) [77]. Like the axillary dissection, decision on the area to be dissected is difficult from the viewpoint of local control, overall survival and complications.

Hughes et al. reported that in cases of palpable inguinal lymph node metastases, pelvic lymph node recurrence occurred in one of 72 patients who had DLND and seven of 60 patients who had SLND ($p=0.01$) [74]. In this study, patients with one positive superficial node

and those with more than one positive superficial node were 17% and 51% of 72 patients with DLND respectively. The number of positive superficial lymph nodes and the presence of extracapsular spread were significant prognostic factors for overall survival [77].

In addition, the patients who had DLND with the presence of pelvic lymph node metastases had significantly poorer five year survival than the patients without the pelvic lymph node metastases. However, there was no difference in postoperative morbidity between SLND and DLND [74]. Van der Ploeg et al. also reported that survival and local control did not differ for patients with palpable inguinal metastases treated by DLND or SLND and pelvic lymph node metastases was a significant prognostic factor [78]. In their series of 169 patients with palpable nodes in the inguinal region, five year estimated overall survival rates were 33% for DLND and 29% for SLND.

However, there is no evidence on how the recurrence affects quality of life when DLND is not performed and how the recurrence occurs in the pelvic region for melanomas on lower extremities. It is likely that enlargement of a tumour in pelvic region causes lymphedema, congestion of lower extremities, ileus and so on. Although these symptoms may be due to DLND, also it is possible that DLND increases patients' quality of life during the remaining life time by decreasing the risk of recurrence in the pelvic region. However, there is no evidence indicating this.

Cloquet's node is an indicator of pelvic lymph node metastases. According to Shen et al.'s study, positive pelvic lymph nodes were identified in the DLND specimen from 20 of 30 (67%) patients with a positive Cloquet's node and negative pelvic lymph nodes were identified from 27 of 35 (77%) patients with a negative Cloquet's node ($p=0.0019$) [79].

Pre-operative computed tomography (CT) is also a good tool to use in predicting the metastasis. Out of 44 patients with negative pelvic lymph nodes evaluated with pre-operative CT, 40 patients had in fact histologically negative pelvic lymph nodes (negative predictive value = 90.9%). On the other hand, the positive predictive value of pre-operative CT for pelvic metastases, was 59% [78].

A recent study shows pre-operative lymphoscintigraphy can be used to guide the extent of inguinal lymph node dissection [66]. Chu et al. reported on 42 cases of DLND with positive inguinal SLNs. The frequency of synchronous pelvic disease was five of 42 (11.9%) [80]. All five cases with pelvic disease had primary melanomas on extremities. Upon review on the lymphoscintigraphic findings, pelvic drainage was present in four of five cases with pelvic disease (80%) and in 18 of the 32 cases (56%) without pelvic disease, though neither was statistically significant. This strategy is based on the idea that when lymphoscintigraphy shows secondary nodes to be located in the next drainage basin, this basin should be included as the dissecting area [66]. More data is necessary to prove that treatment based on the idea improves the mortality and local control.

For now, there is no guideline on choosing between SLND and DLND. However, many findings provide useful information and surgeons should actively select DLND when a case falls under any of the following conditions:

- There is a palpable inguinal metastasis.
- There is more than one superficial lymph node metastasis.
- CT indicates metastatic pelvic lymph nodes.
- There is a Cloquet's lymph node metastasis.
- Lymphoscintigraphy indicates SLNs in the pelvic region with a superficial lymph node metastasis.

10. Molecular targeted therapy

Recent discoveries in cell signalling have provided greater understanding of the biology that underlines melanoma and these advances are being exploited to provide targeted drugs and new therapeutic approaches [81]. In some cases of ALM and mucosal melanoma, the mutations of KIT, a transmembrane receptor tyrosine kinase, are reported and these mutations lead to marked expression of KIT in tumour cells. These cases have marked a tendency to respond to imatinib mesylate which inhibits tyrosine kinase. Although case reports are accumulating [82,83], more data, including long-term control and prognostic data, will be necessary to confirm the effect of this agent.

11. Conclusion

Controversies remain regarding the surgical treatment of ALM as described above, thus, international guidelines are yet to be established.

It is not still known whether the thickness of the nail tumour is the same as that on other sites because the distance between the nail bed and bone is very narrow and a mild degree of invasion can reach the bone easily. Considering the poor prognosis of cases with subungual melanoma, the tumour thickness of the subungual melanoma needs to be evaluated. Because biopsies of the nail bed may cause cosmetic and occasionally functional problems, surgeons may hesitate to do biopsies and lose a vital chance of early diagnosis. Suspicious lesions should be actively biopsied with fully informed consent. When taking a wait-and-see approach, careful observation is necessary so as not to overlook any minor change of dermoscopic findings.

On the excision margins around the primary lesion, 2cm is regarded as sufficient for invasive melanomas. Although some guidelines suggest a 0.5 cm margin for melanomas in situ, some data indicated that resection with 0.5 cm margin caused significant high rates of local recurrence. As mentioned here according to the report, a 1cm surgical margin is a better answer for melanomas in situ, except for tumours on cosmetic or functional sites such as the face or fingers. When an excision margin is less than 1cm, more careful histological examination and follow-up are necessary.

Although SLNB is the standard technique for the management of malignant melanoma, the definition of SLN itself has not been established. This creates differences in the extent of SLNB between each institute. SLNs in patients with melanomas on upper extremities are very rarely located in level 3. There are very few cases with positive SLNs only in level 3 without positive SLNs in level 1 or 2, thus, the lymph nodes in level 3 can be regarded as secondary nodes for melanomas on upper extremities in almost all cases. Surgeons should also pay additional attention to SLNs in other sites such as supraclavicular, the cubital region and interval nodes.

There is controversy around the management of lymph nodes in the pelvic region. According to the literature, there were patients without positive SLNs in the inguinal region, who had metastatic lymph nodes in the pelvic region during follow-up. Thus, at the moment, it is better not to regard all pelvic lymph nodes as secondary nodes and not to exclude all pelvic lymph nodes from SLNs. There are no reported cases with primary melanomas below the knee in which only positive pelvic lymph nodes are present without positive inguinal lymph nodes. Thus, surgeons should decide whether to harvest pelvic lymph nodes taking into consideration the sites of primary lesion, Breslow thickness and the possibility of complication on a case by case basis.

Whether or not dissection in cases with primary lesions on upper extremities should include the extent of level 3 is controversial. When a case falls under any of the lists described above, the dissection including level 3 should be actively performed. However, not all cases with positive lymph nodes in level 1 or 2 need to undergo dissection including level 3.

Similarly, it is difficult to choose between SLND and DLND in the case of primary melanomas on lower extremities. The cases which are likely to have metastatic lymph nodes in the pelvic region were mentioned above. It is better that the indication of DLND is determined by referring to the list.

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