

## **Sentinel node biopsy in Japan**

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## **Abstract**

Similar to western countries, intraoperative lymphatic mapping and selected lymphadenectomy (SNB) have been verified and are widely performed for staging of melanoma in Japan. Recent studies showed that approximately 90% (73/81) of university hospitals and several cancer hospitals routinely perform SNB, and half of melanoma patients receive this examination. SNB is performed according to a variation of the standard procedure described by Morton and Cochran. The most frequently used tracers are Tc<sup>99m</sup>-tin colloid or Tc<sup>99m</sup>-phytate for scintigraphy and patent blue violet or indigo carmine as a blue dye. Some institutions use indocyanine green, which is fluorescent and can be used to visualize sentinel lymph node(s) (SN) under an infrared camera. The recent detection rates of SN has increased to over 95% with the method using blue dye, lymphoscintigraphy, and a handheld gamma probe. In a multicenter study, the rates of metastasis in SN were as follows: pTis, 0% (0/36); pT1, 11.3% (6/56); pT2, 21.0% (13/63); pT3, 34.0% (35/103); and pT4, 62.4% (63/101). Metastasis rate was also significantly related with ulceration of the primary tumor. Here, we discuss data from Japanese patients and the present status of SNB in Japan.

## **Introduction**

Lymph node metastasis is one of the most powerful predictors of recurrence and survival in patients with melanoma<sup>1</sup>. Therefore, elective lymph node dissection (ELND) has been widely used in the treatment of these patients. However, in several randomized controlled trials, overall survival benefits of ELND were not confirmed and ELND is becoming less common, especially in the USA<sup>2</sup>. In Japan, ELND had been accepted as the standard management in patients with primary tumors more than 3 mm in thickness.

Intraoperative lymphatic mapping and selected lymphadenectomy (SNB) have made it possible to determine the lymphatic flow from a primary tumor and to identify its sentinel lymph node(s) (SN) in the regional basin<sup>3,4</sup>. This technique not only has lower morbidity than ELND but also permits more accurate and reliable staging. The new UICC/AJCC melanoma staging system has incorporated the pathological evaluation in SN into the new staging criteria for melanoma<sup>1</sup>. SLNB has been verified and is widely used as staging tool for melanoma in Japan. Here, we mainly discuss data from Japanese patients and the present status of sentinel node biopsy in Japan.

## **Melanoma in Japan**

The incidence of skin cancer in Japan is lower than in the USA, Australia, and Europe. However, similar to these other countries, the number of cases of skin cancer is gradually increasing (Figure 1). This is most likely due to the aging demographic of the Japanese population. Half of all patients that die of skin cancer have melanoma, and the number of such cases was 539 (male, 281; female, 258) per year in 2005 in Japan. This corresponded to only 0.17% of the patients who died from cancer in all organs. The crude and age-adjusted mortality rates of melanoma per 100000 were approximately 1.0 and 0.5, respectively. Melanoma has initially been diagnosed in approximately 1500 patients per year and its rate is increasing. A study by the Prognosis and Statistical Investigation Committee (PSIC) of the Japanese Skin Cancer Society (JSCS) showed that the numbers of patients with malignant melanoma in 22 hospitals over several years were 1717 (1987 – 1991), 1991 (1992 – 1996), and 2468 (1997 – 2001)<sup>5</sup>. Trends in anatomical site and Clark's subtype in Japan are shown in Tables 1 and 2<sup>6</sup>. The foot is the most prevalent site of these lesions, and acral lentiginous melanoma is the most common type in Japanese patients. The prognosis of Japanese patients with melanoma is similar to those in western countries. Five-year survival rates according to the new UICC/AJCC-TNM classification in Japanese patients are as follows: stage 1A, 100%; IB, 91.1%; IIA, 81.5%; IIB, 70.1%; IIC, 64.6%; IIIA, 65.6%; IIIB, 61.8%; IIIC, 25.5%; IV, 13.4% ( $n = 342$ )<sup>7</sup>.

## **History of SNB in Japan**

Since 1988, several Japanese researchers have studied the lymphatic pathway and lymph node(s) drained from primary melanoma<sup>8</sup>. Morton et al.

reported the concept of SN and sentinel node navigation surgery in 1992, and it has since been used by dermatologists and plastic surgeons in Japan<sup>3</sup>. There have been several Japanese reports regard SNB since the late 1990s<sup>9-12</sup>. The first meeting regarding SNB for management of melanoma in Japan was held in November 1999 (Sentinel Node Mapping and Dissection in Staging and Treatment. Chairs: Cochran AJ and Saida T, Satellite meeting 4, 17<sup>th</sup> International Pigment Cell Conference, Nagoya, Japan). At this meeting, a practical method and concept regarding SNB were described by research pioneers from the USA, Australia, and Japan. Since the early 2000s, SNB has become widely used by dermatologists and plastic surgeons in association with radiologists, pathologists, and surgeons. A recent study performed in 2007 by the Japanese Dermatological Association indicated that 90% (73/81) of university hospitals and several hospitals specializing in cancer routinely performed SNB (Researchers: Furue M<sup>1</sup>, Saida T<sup>2</sup>, Moroi Y<sup>1</sup>, Uhara H<sup>2</sup>, 1:Department of Dermatology, Graduate School of Medical Science, Kyusyu University, 2: Department of Dermatology, Shinshu University, School of Medicine). Another recent nationwide survey performed by PSIC from 2006 to 2007 in 1058 patients from 160 institutions showed that 45% of all melanoma patients received SNB<sup>6</sup>.

### **Methods of SLNB in Japan**

The combination method using blue dye injection, lymphoscintigraphy, and a handheld gamma probe has been widely used in Japan. However, the SNB procedures, including patient selection, type of tracer used, and pathological evaluation, vary among hospitals. Therefore, the methods described here are mainly those adopted in the ongoing multicenter trial (Evaluation of safety and usefulness of sentinel node biopsy in patients with malignant melanoma, Grant-in-Aid for clinical trial from the Ministry of Health, Labor, and Welfare, Chief researcher, Saida T: H19-clinical trial-013) and/or those used in our hospital.

#### **Patient selection**

SNB is performed essentially according to the standard procedure described by Morton and Cochran<sup>4</sup>. However, there are a few differences between Japan and western countries. In Japan, most patients with melanoma visit our dermatologist or are referred to us from their general practitioner without biopsy of the primary tumor. Preoperative biopsy is usually performed only when clinical diagnosis is difficult. Therefore, the patients generally receive both curative wide resection of the primary tumor and SNB concurrently without prior biopsy. Under these conditions, the thickness of the primary tumor is unknown before SNB. Therefore, in practice, cases with suggested dermal invasion, even those less than 1 mm thick, often become candidates for SNB. Preoperative high-frequency ultrasound may be used to determine the accurate tumor thickness (Figure 2)<sup>13</sup>. Dermoscopy is also useful to predict dermal invasion<sup>14</sup>. On the other hand, it is still controversial

whether patients with lesions over 4 mm in thickness should undergo SNB because historical data indicated that these patients have a high rate of occult systemic metastasis at the time of initial presentation. The European Association of Nuclear Medicine-European Organization for Research and Treatment of Cancer (EANM-EORTC) recommend that SNB should be offered to patients with clinically localized disease, including melanomas over 4 mm in thickness<sup>15</sup>. In the institutions included in the present study, patients with melanomas > 4 mm thick were often candidates for SNB.

#### Lymphatic mapping and node biopsy

Patients with suitable indications for SNB undergo lymphoscintigraphy one day before or on the day of surgery. Radionuclide is injected intradermally around the primary site. Tc<sup>99m</sup>-tin colloid and Tc<sup>99m</sup>-phytate, which have particle sizes ranging from 400 to 5000 nm and from 200 to 1000 nm, respectively, are frequently used as radioactive tracers in Japan. Detection rates by these radionuclides are high, and were reported as 95.2% for tin colloid (99/104) and 98.7%(151/153) for phytate (H19-clinical trial-013). Figure 3 shows combined images from single-photon emission computed tomography and computed tomography. Three-dimensional images allow accurate visualization of the sentinel node(s) (SN) and are especially useful in the head and neck region<sup>16</sup>.

Based on the results of lymphoscintigraphy and handheld gamma probe survey, the site with the highest level of radioactivity is marked with a pen. After anesthesia, patent blue violet or indigo carmine is injected intradermally around the primary tumor and the area is gently massaged to enhance lymphatic flow. When an incision is made over the marked skin site and the SN is identified with a handheld gamma probe and visualized by blue dye. Some hospitals use fluorescent indocyanine green, which allows visualization of the SLN with an infrared camera. A clinical trial to evaluate the efficacy of this method is currently underway. Preliminary results indicate a detection rate of SLN by this method of 100% in 28 cases (Yamazaki N, Dermatology, National Cancer Center Hospital: H19-clinical trial-013). There is no consensus about a practical definition of SN. In our study, lymph node(s) showing over one tenth the radioactivity of the most active node is defined as the SN, although low-activity lymph nodes near SN may also be sometimes excised.

#### Pathological evaluation

The excised SLN is fixed in formalin, embedded in paraffin, and processed for pathological examination according to Cochran's method<sup>4</sup>. The presence of metastases is evaluated using serial sections stained with hematoxylin and eosin (H&E) and the murine monoclonal antibodies Mart1 (MelanA), HMB-45, and S-100 for immunohistochemical evaluation. If the SLN contains metastases, curative lymph node dissection (CLND) is recommended and performed in the majority of cases. Genetic analysis using

RT-PCR to detect much earlier metastasis in SN has been performed since the late 1990s<sup>17</sup>. A clinical trial is currently underway to evaluate the benefits of this approach (Genetic diagnosis of sentinel lymph nodes in malignant melanoma The Grant-in-Aid for clinical trial from the Ministry of Health, Labour, and Welfare, chief researcher, Moroi Y, H19-clinical trial-018).

In Japan, dermatologists and some plastic surgeons are generally involved in almost all steps described above, including injection of tracer, marking of hot spots, lymph node biopsy, resection of primary tumor, pathological evaluation, and even CLND in some hospitals with radiologists, pathologists, and surgeon.

### **SNB data in Japanese patients**

There have been no large-scale studies of melanoma, such as randomized controlled trials, in Japan due to its low incidence. Therefore, we mainly present data from the Melanoma Study Group of the Health and Labour Science Research Grants from the Ministry of Health, Labour, and Welfare (MSG11-7, 15-10, 19-7) and H19-clinical trial-013.

#### **Detection rate**

The data of MSG 11-7 and MSG 15-10 are shown in Table 3. From 1999 to 2002, only vital blue dye was mainly used to detect SLN. Preoperative lymphoscintigraphy was used in one quarter of the patients. In this study, the numbers of SN detected were: 1 in 70% of patients, 2 in 23%, and > 3 in 7%. The detection rate was influenced by the location of the primary site, and was 93% in the groin region, 88% in the axilla, and 78% in the head and neck. The same trend was reported by Takahashi et al., but detection rates were 97% in the groin, 96% in the axilla, and 89% in neck region by a combination of blue dye and radionuclide<sup>18</sup>.

MSG 11-7 reported that metastasis in SN was detected in 25% (65/261) of cases. This study included 130 patients undergoing both elective lymph node dissection and intraoperative lymphatic mapping, which was performed during training of the SNB procedure. In 3 of these 130 cases, metastasis was detected in non-SN but not in SN showing radioactivity and/or staining with blue dye. Therefore, the false negative rate in this study was 2.3%, which confirmed the accuracy of SNB. The data from 2003 to 2007 in MSG 15-10 showed that the combination method with blue dye, lymphoscintigraphy, and the handheld gamma probe had been widely used (Table 3). The detection rate increased from 85% with blue dye only to over 98% with the combination method. Noro et al. reported similar observations in which SLN was detected in 82.4% with blue dye only but in 100% with blue dye and RI<sup>19</sup>. Recently, an interim report showed that detection rate was 97.5% by the combination method (H19-clinical trial-013). These results were similar to those reported previously in western countries.

#### Metastatic rate

The relationship between metastatic rate in SLN and T-categories is shown in Figures 4 – 6<sup>20</sup>. This study was a retrospective review of 259 patients who underwent successful SLN mapping and biopsy in 13 facilities in Japan between 2003 and 2006. Similar to the previous study, the metastatic rate was strongly related to T-category (Figure 4). The relationship between metastatic rate and Breslow's tumor thickness is shown in Figure 5. Metastasis was detected in 4 cases of T1a, excluded as candidates for SLNB in the UICC/ AJCC staging criteria. Tumor thicknesses in these 4 cases were 1.0, 0.8, 0.55, and 0.50 mm. Ulceration increased the rate of metastasis and there was significant difference between T1 – T4 and T1 – T3 groups ( $P < 0.001$ ) (Figure 6).

#### SNB and ELND

The clinical benefit of ELND for patients with melanoma has been controversial. In several randomized controlled trials, overall survival benefits by ELND was not confirmed and ELND has been omitted, especially in the USA. However, in Japan, ELND has been used continuously as standard management in patients with primary tumors > 3 mm thick. Tutsumida et al. compared the outcome of SLND ( $n = 30$ ) and ELND ( $n = 72$ ) in Japanese patients and reported that there was no significant difference in the 3-year disease-free survival rate between the two groups<sup>21</sup>. ELND has been replaced by SNB in many hospitals in Japan.

#### Lymphatic drainage pathway

We can obtain some interesting information through SLNB. For example, the foot is the most prevalent site of melanoma in Japanese patients. There are two main lymphatic routes from the sole of the foot; the fibular route to the popliteal node and the tibial route to the groin node. Clinical experience has shown that popliteal node metastasis is rarely observed in patients with melanoma of the foot and and Tompson et al reported that the rate was less than 1%<sup>22</sup>. We could determine the reason by lymphatic visualization with blue dye. Drainage from the sole of the foot usually passes across the plantar or the dorsal surface of the foot and runs to the dorsal foot branch of the great saphenous vein located on the tibial side before changing direction and passing up along the vein (Figure 7)<sup>23</sup>. Lai et al. reported that the popliteal node received lymphatic flow from a wide region of the foot; the skin of the dorsum of the foot, sole of the heel, and the medial heel<sup>24</sup>. However, in our experience, drainage from the foot to the popliteal node occurs less often except in cases in which groin node metastasis has already occurred.

#### Insurance system and SLNB in Japan

SNB is becoming the standard form of care in early-stage melanoma. Pathological evaluation of SN is now necessary for staging of UICC/AJCC. However, it has been performed as an experimental examination in Japan

and has not yet been approved by the Japanese public health insurance system. However, in 2003, the Ministry of Health, Labour, and Welfare classified SNB as an “advanced medical treatment.” Due to recent progress in medical technology, many advanced treatment methods should be considered candidates for standard care. The aim of “advanced medical treatments” is to evaluate the efficacy and toxicity of new techniques used as standard methods around the world. As technology-related costs in advanced medical treatments are not covered by public health benefits, the patient must pay the costs. However, under the current system, doctors can provide both medical care covered and not covered by insurance at the same time, which is usually prohibited in Japan.

### **Conclusions**

The interim results of the Multicenter Selective Lymphadenectomy Trial (MSCT-I) indicated that early detection of regional lymph node metastasis and subsequent resection contributed to improvement of disease-free survival, although there has been some critical discussion of the analysis of the results<sup>25–29</sup>. SLNB has been verified over a decade and is now widely performed in staging of melanoma in Japan. Recent studies showed that approximately 90% of university hospitals and several cancer hospitals routinely performed SNB and half of the melanoma patients received this examination. The recent detection rates of SN increased to over 95% with the combination method using blue dye, lymphoscintigraphy, and a handheld gamma probe. In the multicenter study in Japan, the metastatic rate in SLN was closely related to tumor thickness and ulceration of the primary tumor. SNB is performed as part of a clinical trial and is not covered by public health insurance in Japan. For approval, some clinical trials are currently ongoing to evaluate the utility and safety of SLNB and to clarify whether quantitative assessment of tumor burden in SLN could become a predictive prognostic factor or an indicator for passing CLND.

### **Acknowledgment**

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## Figure legends

Figure 1: Numbers of patients that died of skin cancer per year and the average age between 1950 and 2005 in Japan. (Plotted from the original data of Aichi Cancer Center, Hospital and Research Center, Chigusa, Nagoya, Aichi, Japan;

Figure 2: Evaluation of tumor thickness by 30 MHz echogram. Tumor thickness in this case was 1.41 mm.

Figure 3: Combined images from single-photon emission computed tomography and computed tomography. SLNs were detected in epitrochlear and axilla regions.

Figure 4: T classification and metastatic rate (%) in sentinel lymph nodes ( $n = 359$ ). (Ref. 20) The numbers of patients with metastasis/total number in each category are shown in parentheses.

Figure 5: Tumor thickness (TT) and metastatic rate (%) in sentinel lymph nodes ( $n = 359$ ). (Ref. 20) The numbers of patients with metastasis/total number in each category are shown in parentheses.

Figure 6: Tumor thickness (TT), ulceration, and metastatic rate (%) in sentinel lymph nodes ( $n = 357$ ). (Ref. 20)

Figure 7: Lymphatic drainage from the sole of the foot visualized by lymphangitis and blue dye injection. Drainage ran to the tibial side and passed up along the foot branch of the great saphenous vein. Closed arrows, lymphangitis; open arrows, blue dye injection. (Ref. 23)

Table 1: Locations of melanomas in Japanese patients (2006 – 2007,  $n = 1053$ ) (Ref. 6)

Table 2: Clinical type of melanoma in Japanese patients (2006 – 2007,  $n = 1053$ ) (Ref. 6)

ALM: acral lentiginous melanoma, NM: nodular melanoma, SSM: superficial spreading melanoma, LMM: lentigo maligna melanoma.

Table 3: Mapping methods and detection rates from 1999 to 2007

B: blue dye, LS: lymphoscintigraphy, P: hand-held gamma probe

\*The Grant-in-Aid for Cancer Research (11-7) from the Ministry of Health, Labour and Welfare, Chief researcher: A Yamamoto (Dermatology, National Cancer Institute Central Hospital)

\*\*the Grant-in-Aid for Cancer Research (15-10) from the Ministry of Health,

Labour and Welfare, Chief researcher: T Saida (Department of Dermatology,  
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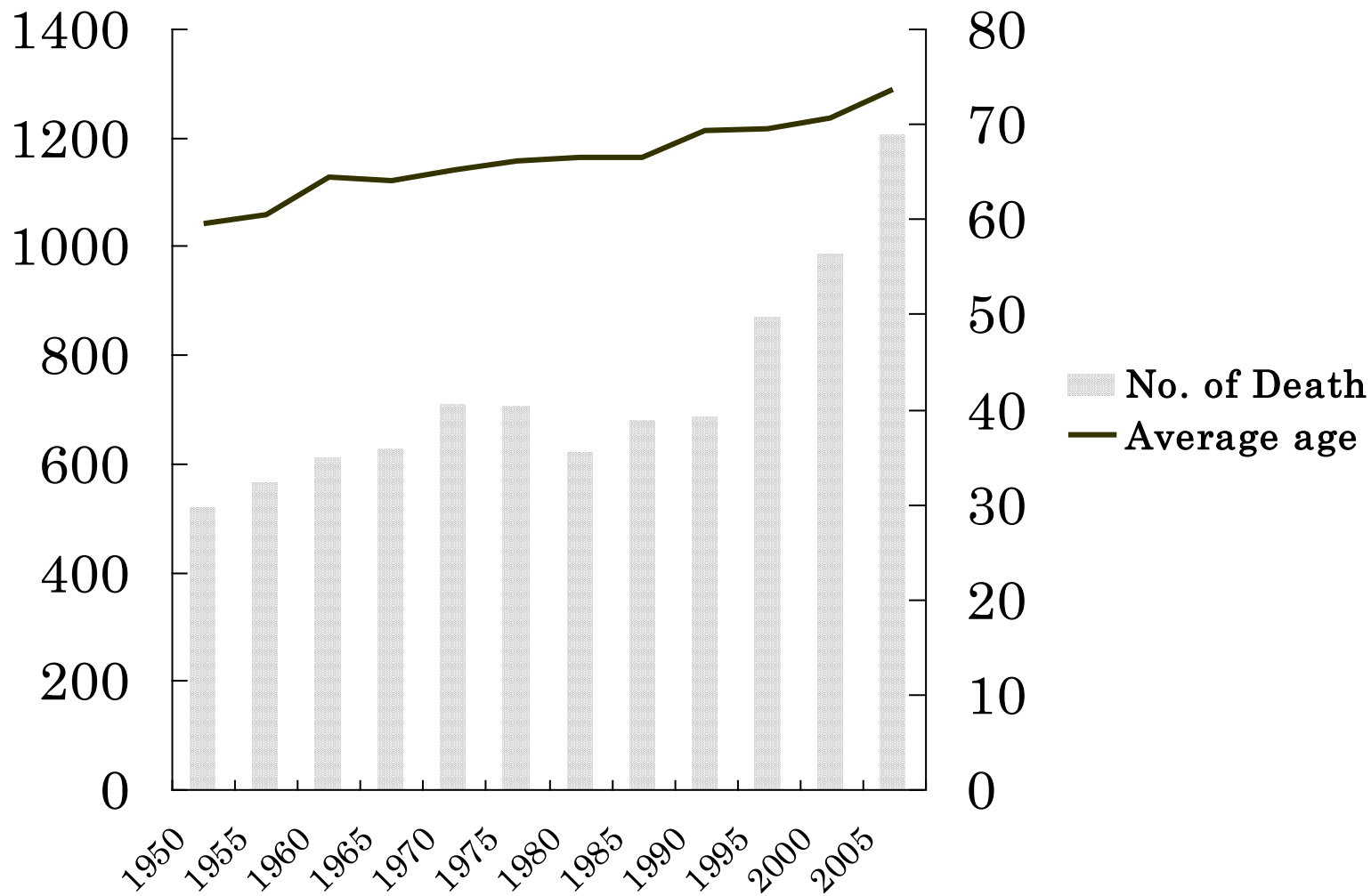


Figure 1



Figure 2:

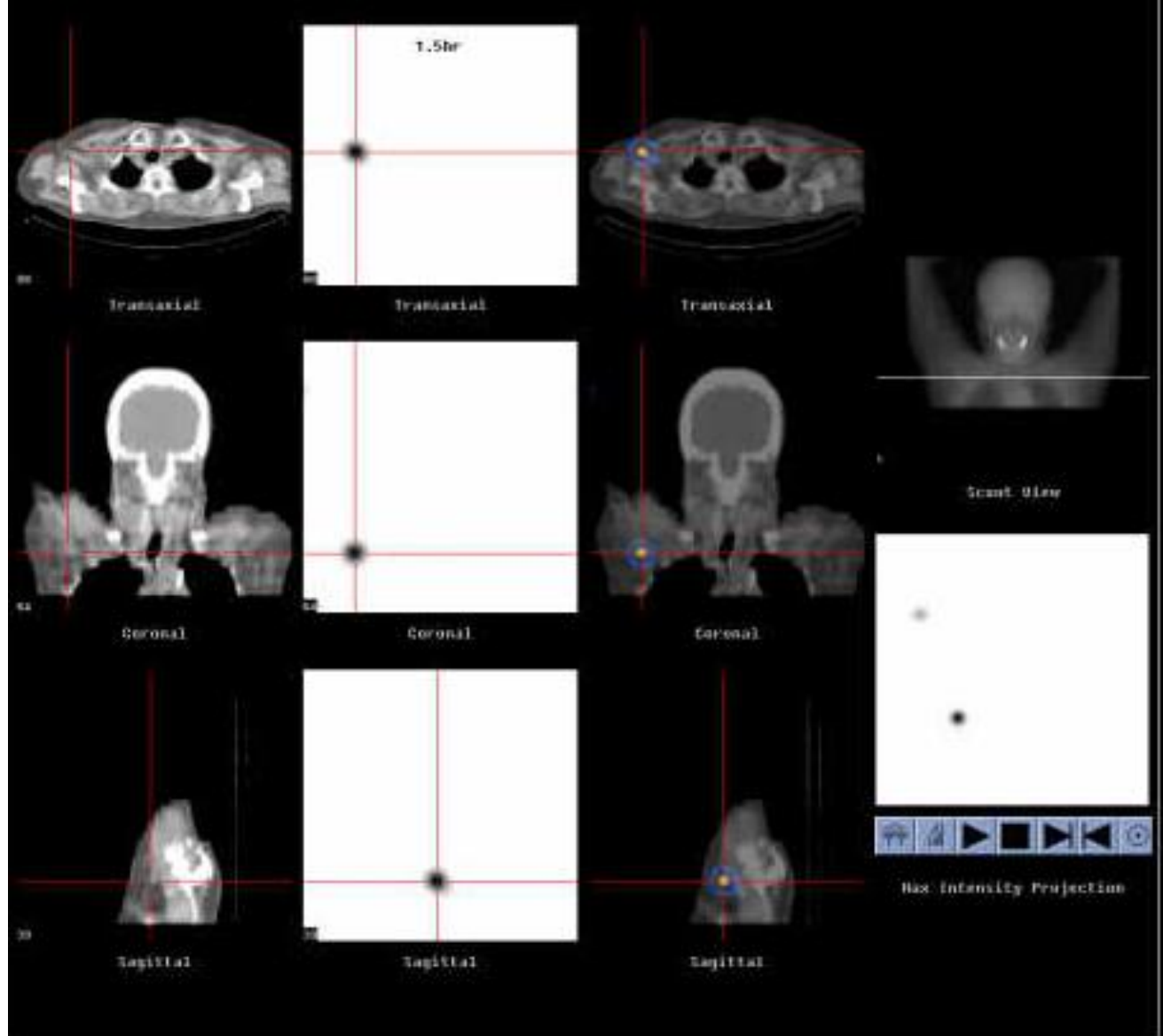


Figure 3

Figure 4

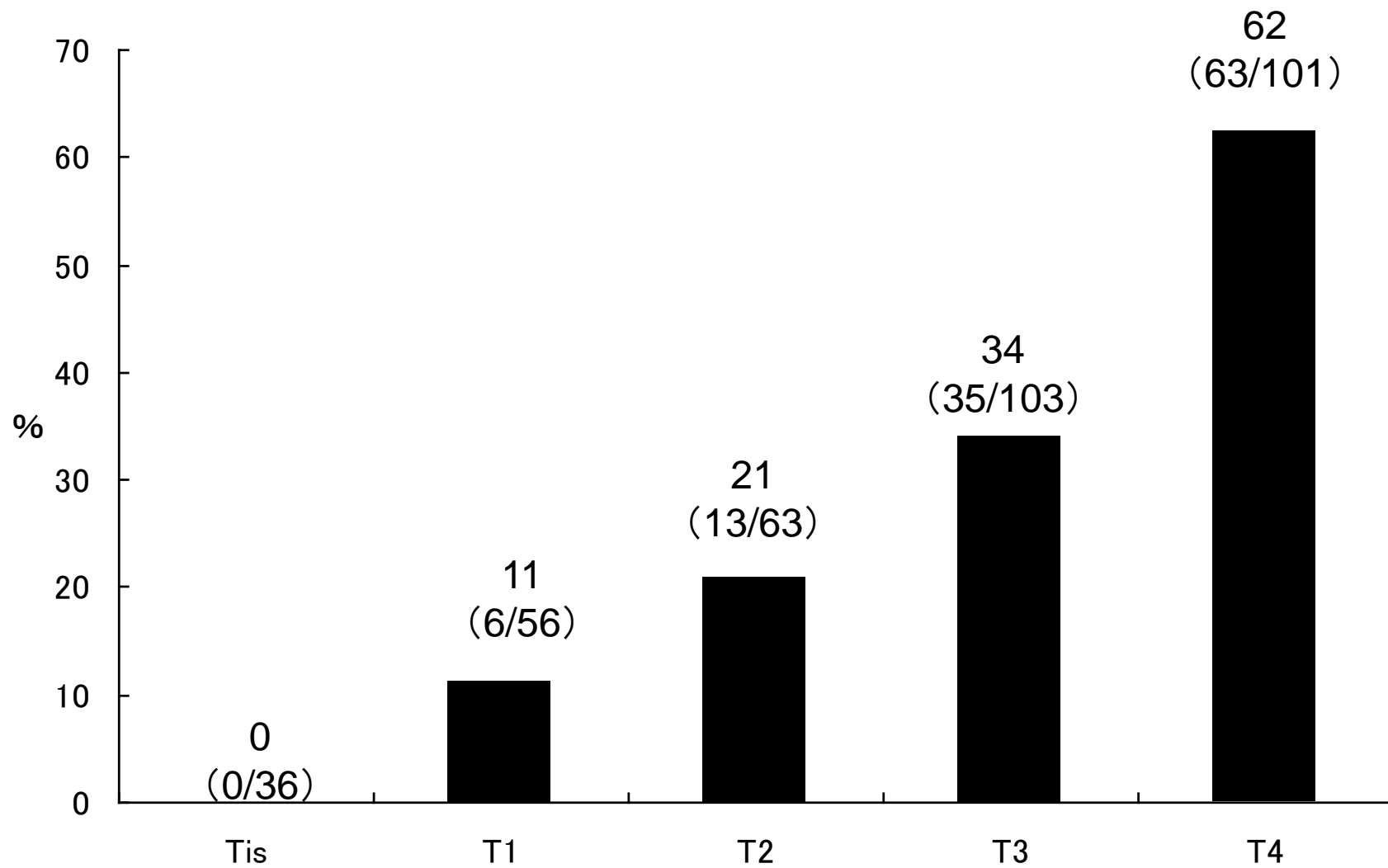




Figure 5

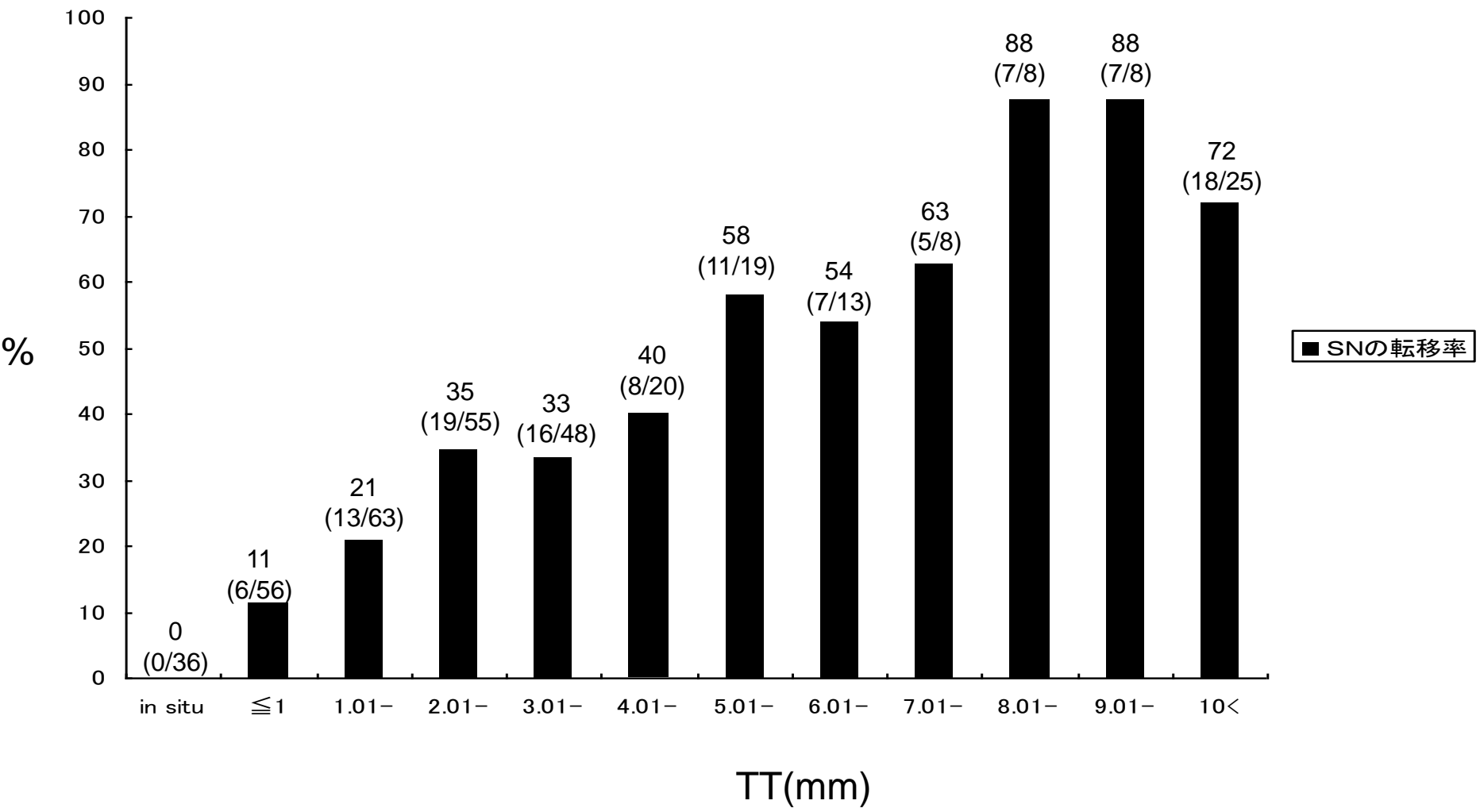
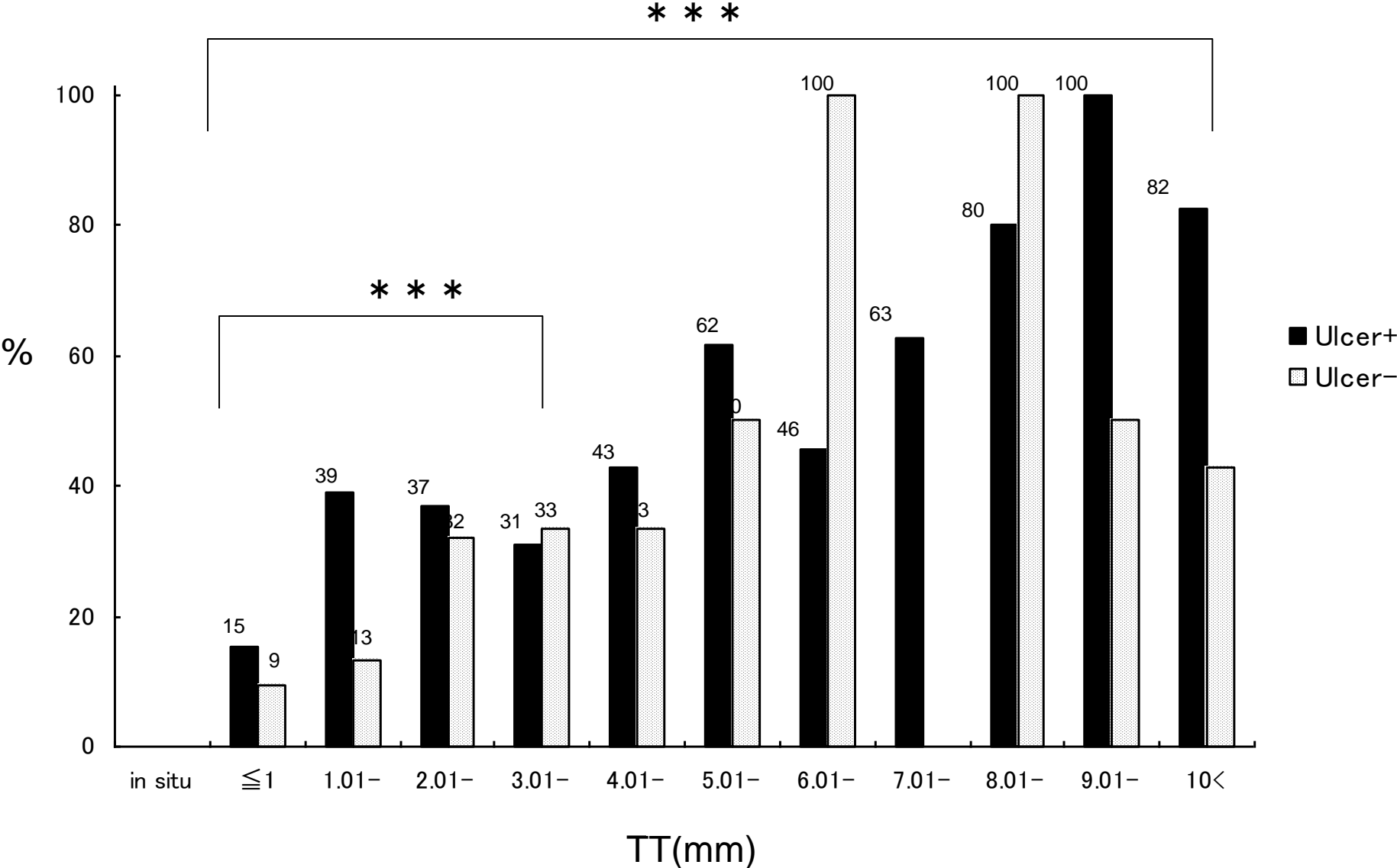


Figure 6



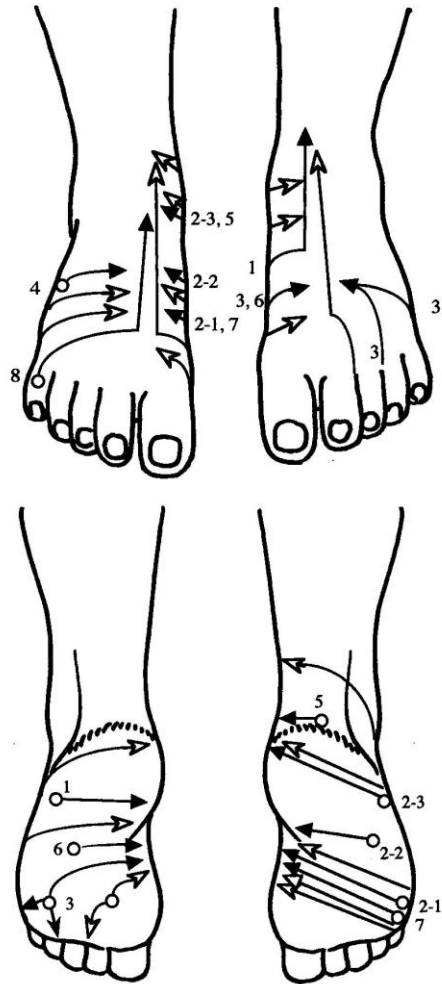


Figure 7

Table 1: Location of melanoma in Japanese  
2006-2007 (n=1053) (Ref. 6)

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Location	%
Foot	42
Body	14
Head & neck	14
Hand	12
Lower limb	9
Upper limb	5
Mucosa	3

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Table 2: Clinical type of melanoma in Japanese  
2006-2007 (n=1053)

Clinical type	%
ALM	51
NM	21
SSM	17
LMM	8
Others	3

ALM: acral lentiginous melanoma, NM: nodular melanoma,  
SSM: superficial spreading melanoma, LMM: lentigo maligna  
melanoma.

Table 3 The mapping methods and detection rate from 1999 to 2007

	1999-2002*	2003-2007**
	Case No / detection rate	Case No / detection rate
B	235 / 85%	0
B+LS	48 / 83%	44 / 84%
B+LS+P	26 / 100%	262 / 98.9%
LS+P	3 / 67%	24 / 100%

B: blue dye, LS: lymphocintigraphy, P: hand-held gamma probe

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