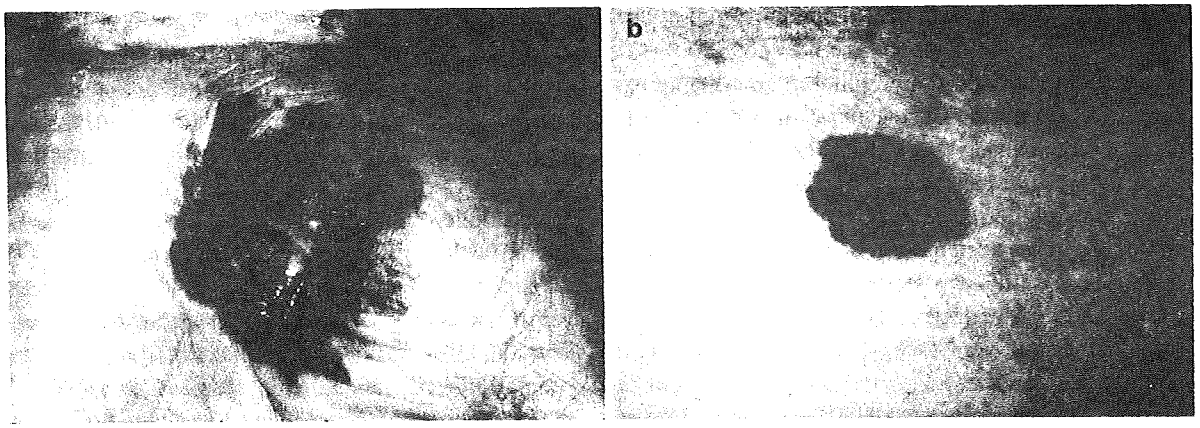


Fig. 11.2.1 Clinical features of primary malignant melanoma. Advanced malignant melanoma is easy to diagnose, because it is clinically seen as a large, irregularly shaped, brownish black lesion often accompanying ulcerated nodules as presented in this lesion on the palm (**a**). In contrast, early melanoma is usually seen as a rather small, brownish black macule (**b**), resembling melanocytic nevus. However, the early melanoma is characterized by irregular shapes with notching and uneven, disorderly pigmentation as seen in this case. This lesion was melanoma in situ seen on upper back of a 25-year-old female. The size was 11 mm in maximum diameter

D1 [9]. Bastian's classification seems to support validity of Clark's classification. However, note that, in Bastian's classification, there is no category of nodular melanomas (NM) in Clark's classification. Furthermore, 5 of 36 acral melanomas in Bastian's series were SSM according to Clark's classification. Therefore, in a sense, Bastian's classification can be considered to support the unifying concept proposed by Ackerman. Bastian's new classification could be considered to ablate Clark's classification and Ackerman's concept in a new dimension [60].

11.2.2.2 Clinical Diagnosis and Dermoscopy

11.2.2.2.1 Clinical Diagnosis and Criteria

The ABCDE rules and the Glasgow's 7-point checklist are popular clinical guidelines for detection of malignant melanoma. The Glasgow's checklist emphasizes the changes of lesions [38], whose sensitivity to early melanoma may be low. ABCDE rule is surely effective in differentiating early melanoma from acquired melanocytic nevus [1], but it may be not so effective in differentiating melanoma form basal cell carcinoma and seborrheic keratosis.

Most advanced melanomas are easy to diagnose clinically (Fig. 11.2.1a).

However, to improve prognosis, we must accurately diagnose this neoplasm in the earlier stages (Fig. 11.2.1b).

The following criteria may be helpful in the early detection.

1. Pigmented macule:
   - Variable shades of brown from tan to black
   - Disorderly and asymmetrical distribution of the colors
2. Irregular shape:
   - Asymmetrical overall configuration
   - Notching at the margin, often
3. Larger size:
   - Usually more than 7 mm in maximum diameter at the time of diagnosis (excluding congenital nevus, which is often larger than 7 mm)
4. Uneven margin:
   - Margin of the lesion abruptly stops partly and is indistinct in other parts.

Using the above criteria, we could effectively differentiate early melanoma from so-called Clark nevus (dysplastic nevus) [59].

11.2.2.2.2 Diagnosis with Dermoscopy

Dermoscopy (dermatoscopy, epiluminescence microscopy), a recently introduced non-invasive diagnostic method, is immensely helpful in determining diagnosis of malignant melanoma. Dermoscopy has revealed new valuable criteria for diagnosing malignant melanoma. The most systematic diagnostic procedure in dermoscopy is the two-step procedure proposed in Consensus Net Meeting on Dermoscopy held in 2000 [6]. Other several dermoscopic procedures have been proposed for the detection of malignant melanoma as follows: pattern analysis, ABCD rule [66], 7-point checklist [4], and Menzies' method [42]. Among them, pattern analysis, first proposed by Pehamberger et al. [53] and later revised by Argenziano & Soyer et al. [5], may be most useful; diagnostic sensitivity was almost same among all the methods, but specificity in the revised pattern analysis was superior to other methods [6].

Melanocytic lesions on acral volar skin exhibit unique dermoscopic patterns. Major dermoscopic patterns seen in melanocytic nevus on acral volar skin are the parallel furrow pattern, the lattice-like pattern, and the fibrillar pattern [61, 62]. Among them, the parallel furrow pattern is the prototype (Fig. 11.2.2a) [61].

Other minor dermoscopic patterns of acral melanocytic nevus have been reported such as homogeneous pattern and reticular pattern [39]. In these benign dermoscopic patterns, pigmentation is prominent along the sulci of the surface skin markings, which run in a parallel fashion in this anatomical site. Interestingly, in macular portions of malignant melanoma affecting acral volar skin, the ridges of the skin markings are preferentially pigmented (Fig. 11.2.2b), which was referred to the parallel ridge pattern [51].

The parallel ridge pattern is frequently detected even in the earlier lesions of acral melanoma. In the stage of melanoma in situ, diagnostic sensitivity and specificity of the parallel ridge pattern are 86% and 99%, respectively [63]. Thus, acral melanoma can be effectively detected in the early curable stages by using dermoscopy.

11.2.2.3 Histopathologic and Genetic Diagnosis

Histopathologic differentiation between malignant melanoma and Spitz nevus is most challenging; Spitz nevus is not infrequently misdiagnosed as malignant melanoma and vice versa. Histopathologic criteria for the differentiation have been proposed [3], and typical cases can be correctly diagnosed by using these criteria. However, Spitz nevus-like lesions with some

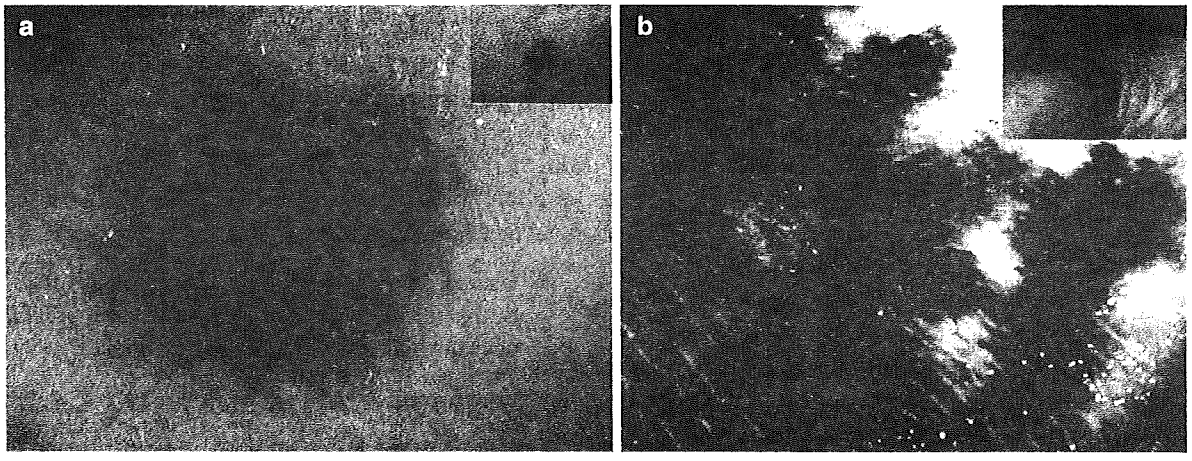
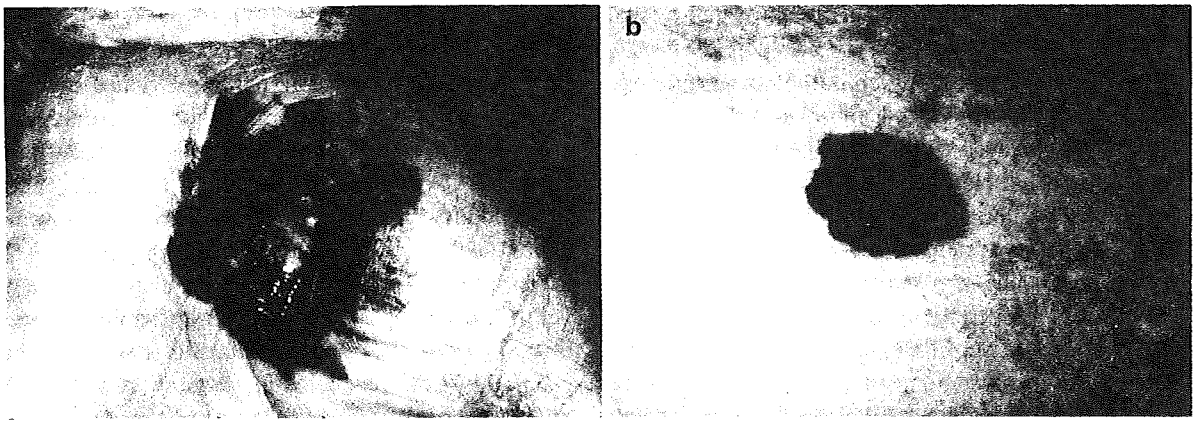


Fig. 11.2.2 Dermoscopic features of melanocytic lesions on acral volar skin. A major dermoscopic pattern most frequently seen in melanocytic nevus on volar skin is the parallel furrow pattern, showing linear pigmentation along the sulci of the surface skin markings (**a**). In contrast, the most characteristic dermoscopic pattern seen in acral melanoma is the parallel ridge pattern, showing band-like pigmentation on the ridges of the skin markings (**b**). Magnification of the dermoscopic images is ×20. Insets are clinical features of each lesion. Both were seen on the sole of the foot.



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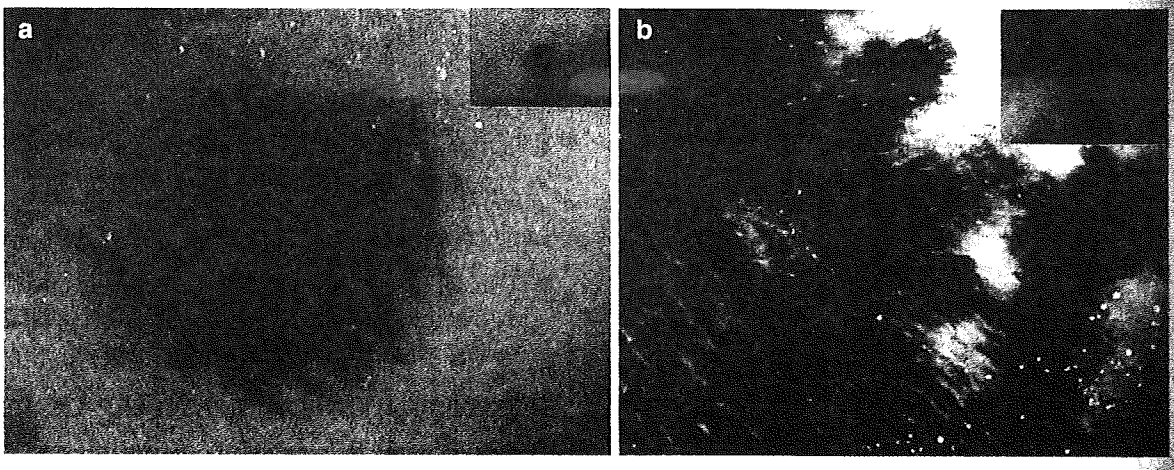

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atypical histopathologic features are not rare, which causes a serious problem in determining diagnosis. Some investigators recently proposed the concept of atypical Spitz nevus and of spitzoid melanoma [8, 11]. According to them, atypical Spitz nevus is a borderline lesion between Spitz nevus and melanoma and spitzoid melanoma is a biologically low-grade melanoma with limited potential of metastasis. Ackerman rejected such ambiguous entities and insisted that diagnosis must be melanoma or Spitz nevus [45]. Gill et al. reported that Spitz nevus and spitzoid melanoma were similar in genetic changes, both did not exhibit B-RAF mutations, which is common in ordinary malignant melanoma [26]. In contrast, van Dijk et al. reported that Spitz nevus and spitzoid melanoma were significantly different in mutation status of B-RAF, N-RAS, and H-RAS (Harvey rat sarcoma viral oncogene homolog) genes [69].

We analyzed a total of 16 spitzoid lesions showing ambiguous histopathologic features. We examined hot spots of mutation in the B-RAF, N-RAS, and H-RAS genes by PCR-based direct sequencing. In addition, we analyzed DNA copy number aberrations and the methylation in cancer-related genes by using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) [68]. Two dermatopathologists independently interpreted a HE stained section of the cases. The two pathologists mostly agreed in the diagnosis of melanoma, however, most lesions diagnosed as Spitz nevus by one pathologist were interpreted as atypical Spitz nevus by the other. Cases diagnosed as melanoma exhibited mutations of B-RAF or N-RAS genes, and/or copy number aberrations of oncogenes or methylation of tumor suppressor genes. In contrast, in almost all cases diagnosed as Spitz nevus or atypical Spitz nevus, no genetic abnormalities were detected. These results indicate that atypical Spitz nevus is nothing but a kind of Spitz nevus.

11.2.3 General Therapeutic Outline

11.2.3.1 Staging and Prognosis

A new staging system of cutaneous melanoma was proposed by American Joint Committee on Cancer staging system (AJCC) in 2001 [7], which was adopted in Union Internationale Contre le Cancer (UICC) staging system in 2002. The TNM classification and the staging system are shown in Table 11.2.1. Key revised points are change of T classification criteria (from 0.75, 1.5 and 4 mm to 1, 2, and 4 mm) and introduction of category of microscopic metastasis in regional lymph

Table 11.2.1 TNM classification and stage grouping (UICC 2002). (a) TNM classification

pT classification (primary lesions)
TX: primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)
T0: no evidence of primary tumor
Tis: melanoma in situ
T1a: tumor thickness≤1mm, without ulceration and level II/III
T1b: tumor thickness≤1mm, with ulceration or level IV/V
T2a: tumor thickness>1 mm,≤2 mm, without ulceration
T2b: tumor thickness>1 mm,≤2 mm, with ulceration
T3a: tumor thickness>2 mm,≤4 mm, without ulceration
T3b: tumor thickness>2 mm,≤4 mm, with ulceration
T4a: tumor thickness>4 mm, without ulceration
T4b: tumor thickness>4 mm,with ulceration
N classification (regional lymph nodes)
NX: regional lymph nodes cannot be assessed
N0: no regional node metastasis
N1a: 1 node, micrometastasis (clinically occult)
N1b: 1 node, macrometastasis (clinically apparent)
N2a: 2–3 nodes, micrometastasis (clinically occult)
N2b: 2–3 nodes, macrometastasis (clinically apparent)
N2c: in transit metastasis/satellite(s) without metastatic nodes
N3: 4 or more metastatic nodes, or matted nodes, or in transit metastasis/satellite(s) with metastatic node(s)
M classification (distant metastases)
MX: distant metastasis cannot be assessed
M0: no distant metastasis
M1a: distant skin, subcutaneous, or nodal metastases, normal serum LDH[a]
M1b: lung metastases, normal serum LDH
M1c: all other metastases, normal serum LDH or any distant metastasis, elevated serum LDH

[a]Lactic dehydrogenase

Table 11.2.1 (b) Stage grouping and 5-year survival of each sub-stage

Stages	Definition of the stage	5-year survival rate[a]	
		Western	Japanese
IA	T1aN0M0	95%	100%
IB	T1bN0M0, T2aN0M0	90	91
IIA	T2bN0M0, T3aN0M0	78	82
IIB	T3bN0M0, T4aN0M0	65	70
IIC	T4bN0M0	45	65
IIIA	T1a-4aN1a-2aM0	67	66
IIIB	T1a-4aN1b,2b,2cM0	53	62
IIIC	T1b-4bN1b,2bM0, anyTN3M0	26	26
IV	anyTanyNM1	12	13

[a]Cited from [7, 50]

nodes, which is evaluated by the sentinel node biopsy. In addition, stage III is defined only as the stage with regional lymph node metastasis, irrespective of microscopic or macroscopic. Sub-stage categories are important in the new staging system. Based on data of 17,600 melanoma patients, 5- and 10-year survival rates of each sub-stage were presented [7], which surely aid in predicting survival of each patient. These survival rates were calculated from data of Caucasian melanoma patients. We investigated survivals of Japanese melanoma patients according to the new staging system (Table 11.2.1). Survival rates are mostly comparable between Balch's series and ours, however, in sub-stages IIC and IIIB, survival rates of Japanese patients seems to be superior [50].

11.2.3.2 Clinical Guidelines for Management of Cutaneous Melanoma

In recent years, several clinical guidelines for management of cutaneous melanoma have been proposed from western countries: The National Comprehensive Cancer Network (NCCN) (http://www.nccn.org) and National Cancer Institute Physician Data Query (http://www.cancer.gov/cancer_information/pdq/) from U.S.A., Guidelines from the Government of Australia (http://www.nhmrc.gov.au/publications/subjects/cancer.htm), and Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/). Almost all these guidelines are formulated based on the principle of the evidence-based medicine (EBM) [56]. These guidelines surely help physicians in the management of melanoma patients.

11.2.4 Current Therapies and Management

11.2.4.1 Surgical Treatment of Primary Lesions

Several randomized clinical trials have confirmed validity of narrow margin excision of primary melanoma [37]. Table 11.2.2 shows recommended excision margin in the several recent guidelines. Lesions of melanoma in situ are excised with 2–5 mm free margin, primary lesions up to 2 mm thickness are excised with about 1 cm free margin, and lesions more than 2 mm in thickness are excised with about 2 cm free margin.

11.2.4.2 Sentinel Lymph Node Biopsy

Introduction of sentinel lymph node biopsy has great impact on the management of regional lymph nodes [47]. The sentinel node(s) is the regional lymph node(s) first receiving the drainage from a particular anatomical site, which is identified with locally injected tracers such as blue dyes or radioisotope particles. If the sentinel node contains no microscopic metastasis, there is virtually no risk that the remaining regional lymph

Table 11.2.2 Recommended excision margin for primary cutaneous melanoma[a]

Tumor thickness	NCCN	UK	Scottish	NCI-PDQ	AAD	ESMO
In situ	5 mm	2–5 mm	2–5 mm		5 mm	5 mm
≤1 mm	1 cm	1 cm	1 cm	1 cm	1 cm	1 cm
>1 mm,≤2 mm	1–2 cm	1–2 cm	1–2cm	2 cm		
>2 mm,≤4 mm	2 cm	2–3 cm	2 cm		2 cm	2 cm
>4 mm	2 cm	2–3 cm	2 cm	2–3 cm		

[a]NCCN: National Comprehensive Cancer Network

UK: Br J Dermatol 146:7, 2002; Scottish: Scottish Intercollegiate Guidelines Network; NCI-PDQ: National Cancer Institute/PDQ(melanoma); AAD: J Am Acad Dermatol 45:579, 2001; ESMO: European Society of Medical Oncology

nodes contain metastasis, and thus regional lymph node dissection is not necessary. Cochran et al. proposed a standardized histopathologic evaluation method of sentinel node(s) [15]. Status of sentinel node has been confirmed as a significant prognostic factor, and a more recent study suggested that sentinel node biopsy could improve the prognosis of melanoma patients [48].

11.2.4.3 Adjuvant Therapy for High-Risk Patients

Melanoma patients in the stages IIC or III are at high-risk of recurrence after radical surgery. These patients are candidates for adjuvant therapy. A randomized controlled trial performed by Kirkwood et al. revealed that long-term administration of high-dose interferon alfa (IFN-α) (2000×10^4 unit/m^2/day, intravenously, for 1 month and 1000×10^4 unit/m^2, three times per week, subcutaneously, for 11 months) significantly prolonged the survivals of high-risk melanoma patients compared with the control group (overall 5-year survival: 46% vs 37, $P=0.02$) [34]. However, later studies failed to confirm the significance [35]. At least at present, no effective adjuvant therapies for high-risk melanoma patients have been established.

11.2.4.4 Management of Metastatic Lesions

If metastasis is solitary or only a few in number and limited to one organ, feasibility of surgical resection is considered. Surgical resection of such lesions may prolong survival time of the patients to some extent [23]. If metastasis is limited to the liver, intra-arterial chemotherapy using cisplatin (CDDP) or other drugs has some palliative effect on the patients' quality of life [24]. Hepatic arterial chemoembolization is also considered in this situation [41].

Effect of chemotherapy on advanced melanoma with multiple metastases is limited. DTIC is still a standard drug for patients with metastatic melanoma. Treatment schedule is (1) 200–250mg/m^2/day, intravenously (iv), on day 1–5, or (2) 850–1,000mg/m^2/day, iv, on day 1 only, repeated every 3–4weeks as far as tolerable. In fact, however, the response rate by this drug is less than 20% and long term remission is exceptional. In a past decade, new drugs such as fotemustine [31] and temozolomide [44] were introduced, but their benefits were limited, compared with DTIC. A variety of combination chemotherapies were proposed. The Dartmouth regimen (BCDT) consisting of CDDP (25 mg/m^2, iv, on day 1–3, every 3–4 weeks), DTIC (220 mg/m^2, iv, on day 1–3, every 3–4 weeks), carmustine (BCNU) (150 mg/m^2, iv, on day 1, every 6–8 weeks) and tamoxifen (TAM) (20 mg/day, per os) was reported to show high response rate around 50% in advanced melanoma [19], however, later randomized controlled clinical trials failed to confirm superior effect compared with DTIC monotherapy [12]. Another attractive regimen was sequential biochemotherapy, in which combination chemotherapy mainly using CDDP immediately followed by biotherapy using interleukin-2 (IL-2) and IFN-α. Higher response rate more than 50% and up to 20% complete response was reported [33]. However, again, randomized controlled trials failed to confirm superior effect of the sequential biochemotherapy compared with corresponding combination chemotherapy alone [57]. Only one study performed by Eton et al. showed borderline significance in the survival (medium survival time: 9.3 months for chemotherapy alone versus 11.9 months for

biochemotherapy using IL-2 and IFN-α; $P=0.06$) [21]. Note that these combination therapies increased incidence and severity of adverse effects.

Malignant melanoma is also highly resistant to radiation, however, radiation therapy can be used as a palliative therapy [54]. Stereotactic radiosurgery for cerebral metastatic melanoma is a choice of palliative treatment [46]. Pain from bone metastases can be transiently relieved by radiation therapy.

11.2.5 Experimental Approaches

11.2.5.1 Immunotherapy

Many melanoma antigens recognized by cytotoxic T cells (CTL) have been identified and amino acid sequences of peptides presented on HLA-molecules and recognized by T cell receptors were analyzed [55]. Among various kinds of immunotherapies, dendritic cell therapy seems to be most attractive. Dendritic cells derived from peripheral blood of patients are pulsed in vitro with a cocktail of melanoma epitope peptides or an autologous tumor lysate and then re-introduced to the patients. Disappearance of large visceral metastases was episodically reported, however, even in these patients, enlarging metastases or new metastatic lesions were often observed during the treatment [49]. This may be explained by loss of melanoma antigens and/or HLA-class I antigens from melanoma cells. Regulatory T cells also have an inhibitory effect on the functions of CTL. Clinical trials of humanized anti-CTLA-4 antibody, which reactivates CTL, have been conducted worldwide, particularly in combination with DTIC [28].

In a recent study by Rosenberg et al., autologous tumor infiltrating lymphocytes (TILs) were expanded in vitro and then transferred to HLA-A2+ patients, who had been received immunodepleting chemotherapy with cyclophosphamide and fludarabine. Along with the TILs, high-dose IL-2 was administrated to the patients. In this trial, 18 of 35 (51%) patients showed clinical response including three patients of complete response with duration 7–24 months [20]. Remarkably, in responded patients, CD8+ lymphocytes accounted for ~80% in the peripheral blood and percentages of the MART-1-reactive T cells were over 60–75% of $CD8^+$ cells for up to 100 days. In this treatment, however, adverse effects were severe and EB virus-related lymphoma occurred in one patient.

11.2.5.2 Gene Therapy and Molecular Targeting Therapy

Various kinds of gene therapy have been tried for advanced melanoma [64]. However, significant clinical response was not obtained in any these trials. We tried gene therapy using expression plasmid of human IFN-β gene encapsulated in cationic liposomes. The liposomes were injected into the metastatic nodules of melanoma. Effects of this gene therapy were limited [40].

Recently, genetic alterations in melanoma cells have been precisely investigated and several activated or inactivated genes were found [10, 60]. The mitogen-activated protein kinase (MAPK) signaling cascade is activated in most melanoma cells [18, 67]. Clinical trials of molecular targeting therapy using small molecules blocking this pathway have started [25]. Bastian's group recently found that oncogenic mutations in KIT gene were detected in acral and mucosal melanomas. The mutations and/or copy number increases of KIT gene were detected in 36% of acral melanomas [17]. They suggested imatinib methylate, a protein kinase inhibitor, could be useful in the treatment of acral melanoma with the KIT alterations, which was recently confirmed in a case of rectal melanoma [30].

11.2.6 Complications to Avoid

All the new treatment for patients with advanced melanoma must be carried out in a setting of the clinical trial. Possible severe adverse effect must be seriously considered before starting these trials.

Take Home Message

› Malignant melanoma is a curable disease if it is detected it in the earlier stages. All physicians should have knowledge about characteristic clinical features of early melanoma. Advancement in basic immunology and in molecular biology will provide us with new diagnostic and therapeutic modalities for this lethal neoplasm in the near future.

11.2.7 Global Variations

Malignant melanoma shows big racial difference in the proportion of the subtypes as well as in the incidence. Ethnic variations in the melanoma subtypes may have important significance in the management.

In Japan, the DAVFeron therapy is now routinely used as an adjuvant therapy. It consists of combination chemotherapy composed of dacarbazine (DTIC), nimustine (ACNU), and vincristine (VCR) along with intracutaneous injection of IFN-β around the surgical scar of a primary lesion. Melanoma patients at stage III (UICC, 1997) showed significantly higher 5-year survival rate compared with historical controls [72]. However, evidence level of this study is rather low and the effect must be critically evaluated in a randomized trial.

Recently, an expert committee of Japanese investigators has published clinical guidelines for the management of malignant melanoma. In the guidelines, algorithm for management of cutaneous melanoma was also proposed (Fig. 11.2.3). The full guidelines are open on the web-site of the Japanese Dermatological

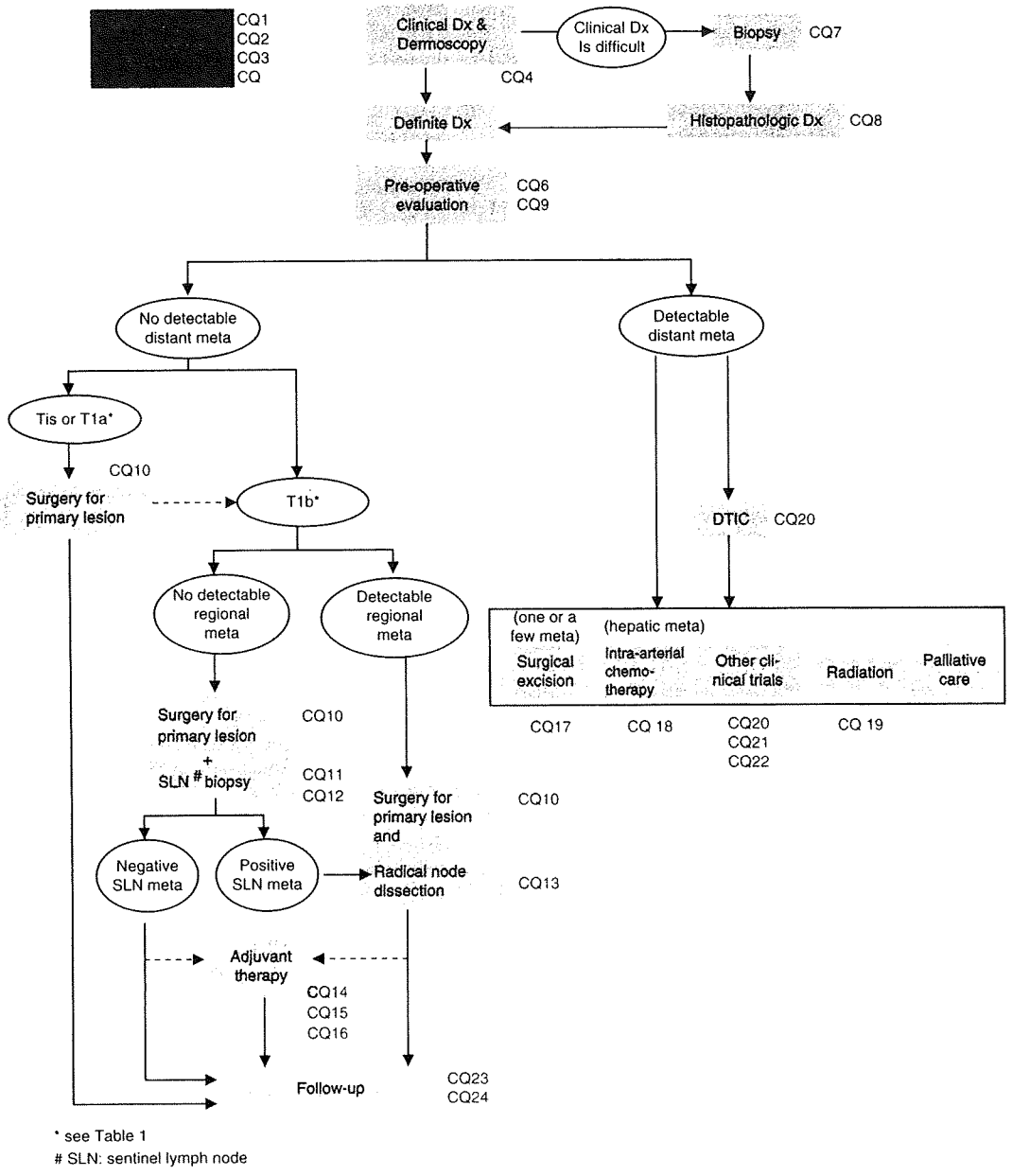

Fig. 11.2.3 Management of malignant melanomas

Association (http://www.dermatol.or.jp/) and a simplified version of the guidelines is seen on the website of the Japan Society of Clinical Oncology (http://jsco.umin.ac.jp/index-j.html). Japanese physicians and 0patients with melanoma can get useful information from the guidelines.

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Thomas Krieg
David R. Bickers
Yoshiki Miyachi (Eds.)

Therapy of Skin Diseases

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Prof. Thomas Krieg
Universitätsklinikum Köln
Klinik und Poliklinik für
Dermatologie und Venerologie
Kerpener Str. 62
50924 Köln
Germany
thomas.krieg@uni-koeln.de

Prof. David R. Bickers
Columbia University
Medical Center
Dept. Dermatology
12th Floor, Herbert Irving Pavilion
161 Fort Washington Ave.
New York
NY 10032
USA
drb25@columbia.edu

Prof. Yoshiki Miyachi
Kyoto University
Graduate School of Medicine
Dept. Dermatology &
Cutaneous Sciences
54 Kawahara-cho
Shogoin, Sakyo-ku
Kyoto 606-8507
Japan
ymiyachi@kuhp.kyoto-u.ac.jp

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（総括・分担）研究報告書）

がん診療ガイドラインの作成（新規・更新）と公開の維持およびその在り方に関する研究

（分担研究者　平尾佳彦・奈良県立医科大学・教授）

研究要旨
2006年に初版を刊行された前立腺癌診療ガイドラインは、前回刊行以後3年の間に、患者数の急速な増加と多彩な治療が導入され、診断・治療に多くのエビデンスが報告され、多くの点において現状に即さない状況になっている。患者数の増加、多彩な治療に加えて、PSA検診の是非が社会的な波紋を及ぼしていることから、診療ガイドラインの早急な改定が求められており、その社会的な意義は大きい。本研究班では日本泌尿器科学会と共同して2010年度末を目標にその改訂作業を行っている。

A．研究目的
前立腺癌は患者数が急速に増加し、多彩な治療が導入され、初版後3年で多くの点において現状に即さない状況になっている。さらにPSA検診の是非が社会的な波紋を及ぼしていることから、診療ガイドラインの早急な改定が求められており、2010年度末を目標にその改訂を行うことを目的とする。

B．研究方法
厚生労働科学研究による診療ガイドライン作成において、各研究者が用いた文献探索式と索引した文献一覧ならびに構造化抄録を全て統括してデジタル保存する作業を行う。文献探索には、前回、会員が作成したソフトウェアを用いることで今後の改定作業は円滑に実施できる。
（倫理面への配慮）
本研究は、文献探索による研究が主体となり、医の倫理には抵触しない。

C．研究結果
1．Minds掲載の前立腺癌診療ガイドライン2006を日本癌治療学会のHPから閲覧できるシステムを作成した。
2．前立腺癌診療ガイドライン2006作成時に使用した文献探索ソフトウェアならびに文献探索式と索引した文献一覧ならびに構造化抄録を全て研究代表者が統括してデジタル保存した。
3．初版ガイドラインで作成したクリニカルクエスチョンを見直しPSA検診、PSA監視療法、化学療法、緩和医療、予防医学などの事項の充実を図る作業を行っている。
4．文献探索は日本医学図書館協会に委託し、文献探索を行っている。

D．考察
過去３年間でPSA検診の是非、新規化学療法、放射線治療の発展に加えてPSA監視療法や緩和医療に多くのエビデンスが集積され、クリニカルクエスションの大幅な見直しが必要になった。放射線治療に関しては日本放射線科専門医会との共同作業が、また化学療法などについては各学会との連携作業が必要である。

E．結論
前立腺癌診療ガイドライン2006は、過去３年間の診断・治療に変遷を必ずしも反映しておらずの改訂は時期を得たものであり、2010年度内に改訂版の刊行が強く求められる。

F．健康危険情報
特になし

G．研究発表
1．論文発表
なし
2．学会発表
改訂作業中で学会では発表していない。

H．知的財産権の出願・登録状況
（予定を含む。）
1．特許取得：なし
2．実用新案登録；なし
3．その他：なし

厚生労働科学研究費補助金
（総括・分担）研究報告書）

がん診療ガイドラインの作成（新規・更新）と公開の維持および その在り方に関する研究

（分担研究者　門田守人・大阪大学・副学長）

研究要旨
分担研究項目である「日本癌治療学会がん診療ガイドライン公開体制の現状と将来」に関する検討を行った。日本癌治療学会におけるガイドライン公開は、診療（治療）アルゴリズム、アルゴリズムに関わるガイドライン説明内容、重要関連構造化抄録の掲載を重点項目としており、現在14がん種の診療ガイドラインが公開されている。今後は、未公開のガイドラインに関しても最新のガイドラインを公開するべく、各専門系学術団体と連携を取り準備を進めているところである。

A．研究目的
日本癌治療学会におけるがん診療ガイドライン公開体制の現状について検討し、その課題と将来の公開体制の在り方を明らかにしていくことを目的とする。

B．研究方法
①日本癌治療学会におけるがん診療ガイドライン公開体制の現状を精査する。②公開体制の課題について検討し、将来の公開体制の在り方に関する考察を行う。
（倫理面への配慮）
該当なし。

C．研究結果
日本癌治療学会としては標準的がん診療内容を国民とともに共有し、共に納得を得ていく機会をつくることを目的に、がん診療ガイドラインの作成促進とそこに記載される標準的診療を公表する事業を計画・推進している。各専門領域の学術団体と連携を形成し、専門領域学会の承認を経て、本学会のがん診療ガイドライン評価委員会での検討を経たがん診療ガイドラインを、ホームページ上において、診療（治療）アルゴリズム、アルゴリズムに関わるガイドライン説明内容、重要関連構造化抄録の掲載を重点項目とし、公表を行っている。現在14がん種の診療ガイドラインが公開されているが、目標である23がん種6診療方法の標準診療ガイドラインに向けて、専門系学術団体と連携を取りながら準備を進めているところである。23がん種および緩和医療のうち、3がん種では診療ガイドラインが存在せず、4がん種ではweb化されておらず、3がん種では当該学会ホームページ上やMindsにおいてのみ公開されており、これらの領域に対する、ガイドラインの作成、web化の支援の在り方や連携の在り方が課題であると考えられた。

D．考察
目標である23がん種および緩和医療ガイドラインの公開に関して、ガイドラインが存在しない3がん種とweb化されていない4がん種に対しては、作成、web化支援の必要性があり、当該学会との更なる連携が必要であると考えられた。すでにweb化されている3がん種では、フォーマットの違いが問題となっており、ある程度統一されたガイドラインのフォーマットが必要であると考えられた。

E．結論
更なるガイドラインの公開に向けて、作成やweb化の支援、ある程度統一されたガイドラインのフォーマットの必要性が示唆された。

F．健康危険情報
特記事項なし。

G．研究発表
1.　論文発表
なし
2.　学会発表
なし

H．知的財産権の出願・登録状況
（予定を含む。）
1. 特許取得
特記事項なし。
2. 実用新案登録
特記事項なし。
3. その他
特記事項なし。

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（分担研究報告書）

がん診療ガイドラインの作成（新規・更新）と公開の維持および その在り方に関する研究
—放射線治療と腫瘍ガイドライン、米国のガイドラインシステム—

（分担研究者　加賀美芳和・国立がんセンター中央病院放射線治療部・医長）

研究要旨
我が国のガイドラインは各医学学会によって作成されている。欧米ではどのような組織がガイドラインを作成しているかを検索し我が国と比較し、欧米でのガイドライン作成の一端を検討した。National Guideline Clearinghouseを使用しRadiotherapyの93ガイドラインの作成機関を調査した。我が国の学会に相当する機関での作成がRadiotherapy guideline 全体の73 %と多数を占めていたが、State/local government agency (US)、State/local government agency (non-US)、National government(non-US) という国または地方自治体が関与する組織での作成も26％を占めていた。欧米でのガイドライン作成は我が国と同様に医学学会が主体となって作成されているが、特にヨーロッパでは国または地方自治体が関与する組織もガイドライン作成に関わっていることがわかった。

A．研究目的
我が国のガイドラインは各医学学会によって作成されている。欧米ではどのような組織がガイドラインを作成しているかを検索し我が国と比較し、欧米でのガイドライン作成の一端を検討する。

B．研究方法
米国Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Servicesでは National Guideline Clearinghouseというデータベースを作成し運営している。現時点で英語で作成されたevidence-basedのガイドラインを約2300集めている。検索、閲覧、比較の機能を有している。今回はこのデータベースにより放射線治療関係のガイドラインがどのような組織で作成されているかを検討した。
（倫理面への配慮）本研究では患者あるいは一般市民へ倫理面を考慮する状況は想定していない。

C．研究結果
閲覧機能でAnalytical, Diagnostic and Therapeutic Techniques and Equipment 2174ガイドラインのうちTherapeuticsは1423でそのうちRadiotherapyは93ガイドラインであった。内訳はBrachytherapy ；22 、Cranial Irradiation ； 3 、Lymphatic Irradiation ； 1 、Radiosurgery ；14 、Radiotherapy Dosage ； 1 、Radiotherapy, Adjuvant ； 71 、Radiotherapy, Computer-Assisted ； 1 Whole-Body Irradiation ； 1 であった。
ガイドライン作成/発刊機関はDisease specific society 13、Medical specialty society 44、Professional association 11 、Private nonprofit organization 1、State/local government agency (US) 1、State/local government agency (non-US) 14、National government(non-US) 9であった。State/local government agency (non-US)、National government(non-US) はカナダ、欧州であった。

D．考察/結論
Disease specific society、Medical specialty society、Professional associationという我が国の学会に相当する機関での作成がRadiotherapy guideline 全体の73 %と多数を占めていたが、State/local government agency (US)、State/local government agency (non-US)、National government(non-US) という国または地方自治体が関与する組織での作成も26％を占めていた。欧米でのガイドライン作成は我が国と同様に医学学会が主体となって作成されているが、特にヨーロッパでは国または地方自治体が関与する組織もガイドライン作成に関わっていることがわかった。

厚生労働科学研究費補助金
（総括・分担）研究報告書

がん診療ガイドラインの作成（新規・更新）と公開の維持およびその在り方に関する研究

（分担研究者　古畑 智久・札幌医科大学外科学第一講座・准教授）

研究要旨　　ESMO、STARTはがん診療に関わる専門医から構成される学術団体であり、NICEおよびSIGNは、政府関連もしく財政的基盤が政府にある研究組織である。ESMO、STARTはがん診療専門医を対象としており、NICE、SIGNは専門医以外の医療者をも対象としていた。対象の違いは、ガイドラインの作成委員の構成、コンテンツ、改訂の頻度に反映されており、それぞれの団体のガイドラインは、特徴を有しているものと思われた。本邦においては、ガイドライン作成は、専門学術団体によってのみ行われているが、包括的公開サイトについては、日本癌治療学会、Minds、がん情報対策センターと複数存在する。今後は、各組織の理念に基づき、各組織と密接な連携を図った上で、特徴ある公開方法を検討していくべきと考えられる。

A．研究目的

欧州におけるがん診療ガイドラインの作成と公開の現状を調査し、本邦のガイドライン作成と公開の在り方について、考察することを目的とする。

B．研究方法

ESMO(European Society of Medical Oncology), NICE (National Institute for Health and Clinical Excellence, England and Wales), SIGN(Scottish Intercollegiate Guidelines Network), START (State of the Art Oncology in Europe, Italy)の4組織の作成するガイドライン作成および公開の現状について検討した。

（倫理面への配慮）

該当なし

C．研究結果

1．作成組織の基盤

ESMO、STARTはがん診療に関わる専門医から構成される学術団体であり、NICEおよびSIGNは、政府関連もしく財政的基盤が政府にある研究組織である。ガイドラインの作成は、医療コストおよび医療制度に関する政策的影響を受けにくい学術団体であることが望ましいが、NICE、SIGNはガイドライン作成において政府からの独立性が保たれていると評価されている。

2．作成委員会の構成

ESMO、STARTは、がん診療に関わる専門家のみによって作成委員が構成されているのに対し、NICE、SIGNは、専門家の他にソーシャルワーカー、ガイドライン作成の方法論の専門家、患者団体の代表などを作成委員会に加えている。ESMO、STARTのガイドラインの対象はがん診療の専門家であり、NICE、SIGNは、がん診療専門家以外の医療者をも対象としていることに起因すると思われる。いずれの組織の作成委員会にも政策および企業の関連者は含まれていない。

3．作成の手法

NICE、SIGNは系統的な文献検索（Systematic review）の定義を満たす手法で作成しているのに対し、ESMO、STARTは定義を満たさない手法で作成されている。ガイドライン作成の方法論の専門家を作成組織に加えているかによる違いと考えられる。いずれの組織も作成委員によるドラフトの作成後に、第3者の評価を受け、段階的な過程を経て公開している。

4．ガイドライン記述形式

ESMO、NICE、SIGN、STARTいずれのガイドラインもテキスト形式が多く、クリニカルクエスチョン形式は少ない。また、診療アルゴリズムを掲載しているガイドラインは少なく、文献の提示のみで構造化抄録の掲載はない。

5．ガイドライン公開方法

学会誌などの紙媒体での公開もあるが、インターネット上の公開が主流であり、紙媒体を必要とする場合は、ダウンロードすることが可能となっている。いずれのガイドラインもパスワード制などのアクセス制限はなく、無料で閲覧可能となっている。その他、各組織の企画する学術集会での公開も行っている。公開の対象は、ESMOとSTARTは欧州全域であり、NICEとSIGNは主に英国である。

6. ガイドラインの改訂
文献の検索を定期的に行うことにより、ガイドラインの改訂を行っている。ESMOとSTARTは毎年、NICEとSIGNは2年毎に行っている。
7. ガイドラインによるアウトカムの評価
ESMO、NICE、SIGNは、ガイドラインによる患者および厚生面でアウトカムの評価を行っているが、STARTでは行っていなかった。
8. 利益相反の記載
利益相反に関する記載は、NICE、SIGNでは公開時から、ESMOは2007年より行われている。STARTに関しては、行われていない。

D. 考察
欧州におけるガイドラインは、学術団体（ESMO、START）と政府関連組織（NICE、SIGN）によって作成されており、それぞれ特徴を有している。学術団体の作成するガイドラインは、がん診療の専門家であり、作成委員もそれを反映して患者団体の代表者などを含めずに専門家のみで構成されていた。一方、政府関連組織は、専門家の他にソーシャルワーカー、ガイドライン作成の方法論の専門家、患者団体の代表などを作成委員に加えている。NICE、SIGNは、がん診療専門医以外をも対象としており、より理解しやすく、実用的なガイドラインを目標としているものと思われる。その他、NICE、SIGNのガイドラインは、系統的文献検索の定義に基づいて作成され、医療コスト、アウトカムの評価、利益相反についての記載など、ガイドラインに要求される事項が含まれており、ガイドライン作成の方法論の専門家を作成委員に加えている結果と思われる。ESMO、STARTのガイドラインは、がん診療専門医を対象としていることから文献の検索を毎年施行しており、NICE、SIGNの2年毎に比べて、その頻度は高い。これは、がん診療専門医を対象としたガイドラインであることから、より最新のエビデンスを迅速に吟味し、情報発信をおこなう学術団体の理念に基づいたものと考えられる。したがって、それぞれのガイドラインの優劣を評価するのではなく、作成対象を認識した上で、ガイドラインを利用することが肝要であると思われる。
本邦において現在公開されているガイドラインは、各がん種の専門学術団体によって作成されており、内容的に学術的に厳正かつ適正に吟味されており、また実用的なガイドラインとなっている。しかしながら、医療コストについての記載、アウトカムの評価、利益相反の記載などが徹底されているとは言い難く今後の課題であろう。また、ガイドラインの改訂の頻度が3~4年となっており、最新の情報の提供が望まれている現状を考えるとESMO、STARTのように毎年の文献検索による一部改訂が必要となってくるであろう。
ガイドライン作成と公開に必要とされる資金源はがん種によって、学術団体のみ、公的資金のみ、これらの両者となっており様々である。本邦での、一つのがん種について一つのガイドラインという現状を考えると、対象が広く、専門医にとっても最新であり、費用対効果の高い多機能なガイドラインが要求されるものと思われる。そのためには、ガイドライン作成の独立性を担保した上で、公的資金による一部助成による専門学術団体による作成が望ましいものと思われる。
本邦でのがん診療ガイドラインのインターネット上の公開は、各専門学術団体のホームページの他に、包括的公開サイトして日本癌治療学会、Minds、がん対策情報センターで行われている。欧州の現状に従えば、日本癌治療学会はがん診療専門医向けのコンテンツ、Mindsおよびがん情報対策センターは、一般臨床医および患者向けのコンテンツとなる。今後は、各専門学術団体とこれら包括的公開サイトをもつこれら3組織が密接な連携を図り、それぞれの理念に基づいた特徴ある公開方法を検討していくべきと思われる。

E. 結論
ガイドラインは、目的と対象によって、内容および公開方法が異なってくるものと思われる。したがって、専門学術団体、日本癌治療学会、Minds、がん対策情報センターが密接な連携を図った上で、特徴ある公開方法を検討していくべきと考えられる。また、ガイドラインに作成に公的資金の助成があった場合においては、政策的な干渉をうけずに独立性が確保されていることが重要である。今後、本研究を通して、具体的な各組織の連携方法を提案していきたい。

F. 健康危険情報
分担研究報告書には記入せずに、総括研究報告書にまとめて記入

G. 研究発表
1. 論文発表
なし
2. 学会発表
① Tomohisa Furuhata・NCCN-JSCO joint symposium・Endeavors of theJSCO to Develop and Present Clinical Practice Guidelines in Oncology・第47回日本がん治療学会学術集会

H. 知的財産権の出願・登録状況
（予定を含む。）
該当なし

特別企画 シンポジウム4 NCCN-JSCO Joint Symposium

Moderators : University of Tsukuba Hideyuki Akaza
Hamamatsu University School of Medicine Seiichiro Ozono
NCCN

第5会場(411+412) 【17:10～19:00】
共催:大塚製薬株式会社/グラクソ・スミスクライン株式会社/塩野義製薬株式会社/大日本住友製薬株式会社/
ノバルティスファーマ株式会社/バイエル薬品株式会社/ファイザー株式会社/ワイス株式会社

SS4-1	Urology and Andrology, Medical Sciences, University of Tsukuba, Japan	Hideyuki Akaza
SS4-2		NCCN
SS4-3	Department of Surgery, Sapporo Medical College, Japan	Tomohisa Furuhata
SS4-4	Department of Urology, Iwate Medical University, School of Medicine, Japan	Tomoaki Fujioka
SS4-5	NCCN-Asia(Hong Kong)	Eric Tan
SS4-6	National Taiwan University, College of Medicine, Cancer Research Center, Taiwan	Ming-Kuen Lai
SS4-7	Urology, Hamamatsu University School of Medicine, Japan	Seiichiro Ozono