

# Dermatology Division

## Introduction

Most of the patients seen by the Dermatology Division are being examined and treated for skin cancer. We also conduct basic research on skin cancer. The number of skin cancer patients in this division is the largest in Japan, as patients are referred from all over the country. Surgery is the main treatment modality for skin cancer, and multi-disciplinary treatments, consisting of chemotherapy, immunotherapy, and radiotherapy, are also routinely carried out in this division. In addition, the division takes the lead in advanced medical treatment for skin cancer all over the country, and plays the most active part in multicenter trials.

## Routine Activities

The division has two staff dermatologists and four residents. In the outpatient clinic, new patients and follow-up patients are seen every day except Tuesday, which is reserved for surgery.

Operations including wide local resection, finger- and toe-amputation, free skin graft, local skin flap plasty, and selective and radical lymph node dissection are mainly performed in the division. Rounds are made and case presentations are held every morning. A division conference is held every Monday to discuss the therapeutic principles for outpatients and inpatients. A clinicopathological conference focusing on surgically removed skin specimens is held with pathologists once a month.

## Research Activities

Malignant melanoma

The Dermatology Division is a center of the melanoma research group in Japan and its work is partly supported by the Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare.

It is extremely important to detect early malignant melanoma lesions accurately and the Dermatology Division adopts dermoscopy for differential diagnosis. Dermoscopy is very useful for the examination of the sole, the most frequent site of Japanese malignant melanoma, since early melanoma frequently shows a parallel ridge pattern, while a parallel furrow, a lattice-like or a fibrillar/filamentous pattern is typical of pigmented nevus.

According to European and American investigators, the absence of metastasis in the sentinel node (SN) indicates no metastasis in other lymph nodes (non-SN) at an accuracy of 98% or higher and saves the need for further prophylactic lymphadenectomy. The Japan melanoma research group carried out a multicenter joint study on SN biopsy and collected and analyzed 275 patients with malignant melanoma. The SN identification rate was 97% with blue dye staining alone. Addition of intraoperative gamma probe to blue dye staining + radioscintigraphy improved the percentage to 97.5% and is recommended as a sure method of identifying SN. Of 198 patients in whom SN was identified and biopsied, 69 (35%) had metastasis and two were false negative cases, i.e. they received lymphadenectomy despite of negative SN and were found to have metastasis in non-SN. The overall accuracy of diagnosis attained to 99%, which was comparable to the data from Europe and America. As the definite pathological diagnosis of SN metastasis is essential, the serial sections of SNs from 125 patients were examined by immunohistochemical procedures using S-100, HMB-45 and Melan A or MART-1. Micrometastasis was detected in six (4.8%) of 125 patients who had been negative for SN metastasis on HE staining of maximum section. This demonstrated that pathological diagnosis of SN should be done carefully by preparing serial sections and making use of immunohistochemical staining.

A phase I clinical study of tumor-specific immuno-

therapy using dendritic cells was conducted in patients with stage IV malignant melanoma. A cocktail of five HLA-A24 or A02 restricted melanoma specific antigen peptides (five peptides each selected out of HLA-A2- and A24-restricted MART-1, gp100, tyrosinase, MAGE-1, -2 and -3 and produced under GMP conditions) was prepared. Immature dendritic cells collected and induced from patients and pulsed with this cocktail were administered subcutaneously to the superficial regional lymph nodes. This immunotherapy was conducted in nine patients, and one patient showed complete remission and another showed partial response. In both responders, marked induction of antigen-specific CD8 was observed and clinical antitumor effect almost coincided with its appearance. No serious drug-induced reactions were observed at all, and the therapy could be conducted safely.

## Clinical Trials

(1) Sentinel node navigation surgery for malignant melanoma and other skin cancer is being assessed using combination method with blue dye staining, radioscintigraphy and intraoperative gamma probe.

(2) Combination chemotherapy consisting of dimethyl-triazeno-imidazol carboxamide, nimustine hydrochloride, cis-diaminedichloro-platinum, and tamoxifen is being assessed for advanced malignant melanoma.

(3) Serum 5-S-cysteinyl-dopa and melanoma inhibitory activity levels as tumor marker of malignant melanoma are periodically measured. We are studying their correlation with the patho-physiological conditions of patients.

(4) With the aim of developing a novel immunotherapy for advancing-stage melanoma, the Dermatology Division has finished a phase I and started a phase II study of a tumor-specific immunotherapy with antigen peptides and dendrite cells. Monocytes are isolated from patient peripheral blood, cultured in the presence of rGM-CSF and rIL-4 and pulsed with some melanoma-specific antigen peptides five peptides each selected out of HLA-A2- and A24-restricted MART-1, gp100, tyrosinase, MAGE-1, -2 and -3 and produced under GMP conditions). Resulting dendrite cells are subcutaneously injected in the vicinity of the superficial lymph nodes.

● A. Yamamoto ●

5-year Survival Rates for Squamous Cell Carcinoma (in new patients treated between 1992 and 2001) (Staging by UICC-TNM 1997)

Stage	I	96.4 %	(n=49)
	II	82.2 %	(n=25)
	III	62.8 %	(n=28)
	IV	52.5 %	(n=10)

Number of New Patients

	2003	2004
Malignant melanoma	74	97
Squamous cell carcinoma	24	31
Basal cell carcinoma	31	47
Sweat gland carcinoma	7	8
Trichilemmal carcinoma	2	0
Paget's disease	13	12
Bowen's disease	7	12
Dermatofibrosarcoma protuberans	3	5
Angiosarcoma	3	3
Malignant fibrous histiocytoma	1	1
Malignant lymphoma	12	12
others	5	4
Total	182	232