

# Sarcoma Research

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Japan Sarcoma Association*

*Topics in this issue  
Proceedings and Reports of  
The Japan-United States  
International Workshop on the  
Sarcoma Research and Therapy*

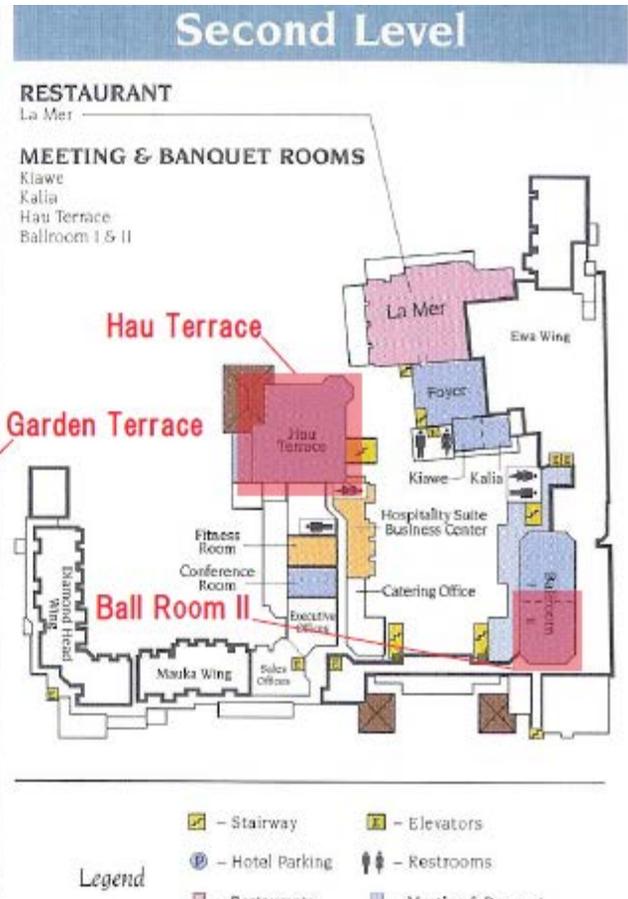
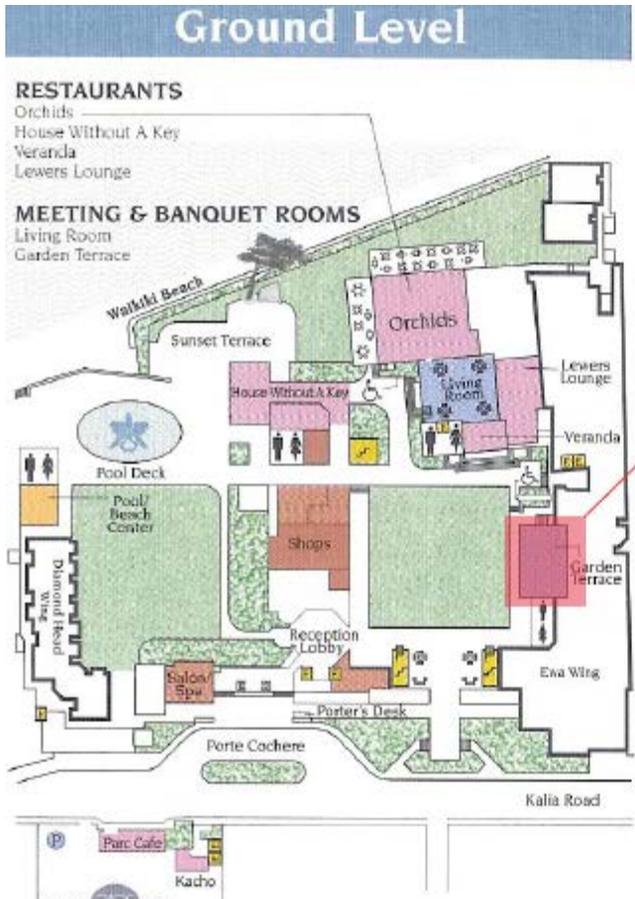
*The Japan-United States  
International Workshop on the  
Sarcoma Research and Therapy  
Kick-Off Meeting for Foundation of  
The Japan Sarcoma Association (JSA)*



*December 4 and 5, 2014  
Hau Terrace, Halekulani  
2199 Kaila Rd. Honolulu. HI 96815, United States*



# Honolulu, Hawaii



- Legend**
- Stairway
  - Elevators
  - Hotel Parking
  - Restrooms
  - Restaurants
  - Meeting & Banquet
  - Guest Facilities
  - Shops

# Floor Map of Halekulani

## Program at a Glance

	December 4 (Thu)	December 5 (Fri)
	Hau Terrace	Hau Terrace
8:00		Buffet Breakfast (Garden Terrace)
9:00	Refreshments Opening/JSA	Frontiers in the Medical Oncology in Sarcoma –Past, Present and Future
10:00	Frontiers in the Genomic Landscape and Histogenesis of Sarcoma	
11:00		
12:00	Luncheon Seminar (Garden Terrace)	
13:00		
14:00	Frontiers in the Surgical Oncology in Sarcoma	
15:00	Coffee Break	
16:00	Leading and Pioneering Topical Treatment of Sarcoma	
17:00		
18:00	Poster Presentation (Ballroom II)	
19:00	Banquet/Gala Dinner (Ballroom II)	
20:00		

# Thursday, December 4, 2014

## 9:00 Refreshments

### 9:30 Opening Remarks

Katsuhito Takahashi, M.D., Ph.D. (Osaka Medical Center for Cancer & Cardiovascular Diseases, Japan)

### 9:45 The Japan Sarcoma Association (JSA)

Satoshi Teraoka, M.D., Ph.D. (International University of Health and Welfare, Japan)

### 10:00 Frontiers in the Genomic Landscape and Histogenesis of Sarcoma

Moderators: Katsuhito Takahashi

(Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan)

Robin L. Jones (University of Washington, U.S.A.)

Whole genome analysis of Ewing sarcoma family tumors.

Andrew Brohl, M.D.<sup>1</sup> and Javed Khan M.D.<sup>2</sup> (1 The Mount Sinai Hospital, 2 The National Cancer Institute)

Histogenesis of Ewing's sarcoma; Modeling fusion gene-associated bone and soft tissue sarcoma

Takuro Nakamura, M.D., Ph.D. (The Cancer Institute, Japan)

### 12:00-13:00 Luncheon Seminar (Garden Terrace)

Moderator: Hiroyuki Narahara

(Hyogo Prefectural Nishinomiya Hospital, Japan)

Clinical evaluation and treatment of leiomyosarcoma

Katsuhito Takahashi, M.D., Ph.D. (Osaka Medical Center for Cancer & Cardiovascular Diseases, Japan)

### 14:00 Frontiers in the Surgical Oncology in Sarcoma

Moderators: Robert Maki (Mount Sinai Hospital, U.S.A.)

Jun Yashima (International University of Welfare and Health, Atami Hospital, Japan)

Challenging surgical treatment of abdominal, retroperitoneal and gastrointestinal sarcoma

Yasuo Ono, M.D. (Fuchinobe General Hospital/Shin-Yamanote Hospital/IUHW Atami Hospital, Japan)

Surgical treatment of multiple lung metastasis of sarcoma

Shinichi Toyooka, M.D., Ph.D. (Okayama University Hospital, Japan)

The surgical management and immunotherapy of retroperitoneal liposarcoma

William W. Tseng, M.D. (University of Southern California, U.S.A.)

### 15:20 Coffee Break at Terrace



### 16:00 **Leading and Pioneering Topical Treatment of Sarcoma**

Moderators: Yu Oyama (Kameda Medical Center, Japan)  
Ryo Hatae (Shin-yamanote Hospital, Japan)

Radio-frequency ablation therapy for multiple liver metastasis of sarcoma  
Yukihiro Koike, M.D., Ph.D. (Kanto Central Hospital, Japan)

Cryo-ablation therapy for multiple lung metastasis of sarcoma  
Hiroaki Nomori, M.D., Ph.D. (Kameda General Hospital, Japan)

Particle radiotherapy (carbon ions and protons) for sarcoma  
Yusuke Demizu, M.D., Ph.D. (Hyogo Ion-Beam Medical Center, Japan)

### 18:00-20:00 **Poster Presentation/ Patient Advocacy/ Banquet-Gala Dinner (Ballroom II)**

Moderators: Yasuo Ono (Fuchinobe General Hospital/Shin-Yamanote Hospital/IUHW Atami Hospital, Jap.  
Hisako Yamamura (Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan)

## Friday, December 5, 2014

### 8:00 **Buffet Breakfast (Garden Terrace)**

### 9:00 **Frontiers in the Medical Oncology in Sarcoma -Past, Present and Future**

Moderators: Satoshi Teraoka (International University of Welfare and Health, Japan)  
Shin-ichi Toyooka (Okayama University, Japan)

**State of the Art Lecture:** Drug therapy for sarcoma –Past, present and future  
Robert Maki, M.D., Ph.D. (Mount Sinai Hospital, U.S.A.)

Chemotherapy and molecular-targeted therapy for sarcoma  
Yu Oyama, M.D. (Kameda General Hospital, Japan)

Pazopanib, an anti-angiogenesis therapy for sarcoma  
Hiroyuki Narahara, M.D., Ph.D. (Hyogo Prefectural Nishinomiya Hospital, Japan)

Recent advances and clinical trials of drug therapy in sarcoma  
Robin L. Jones, M.D., Ph.D. (University of Washington, U.S.A.)

### 12:00 **Closing Remarks**

Robert Maki, M.D., Ph.D. (Mount Sinai Hospital, U.S.A.)



*Thursday, December 4, 2014*

**9:30 (Hau Terrace)**

## **Opening Remarks**

Katsuhito Takahashi, M.D., Ph.D., Organizer  
(Osaka Medical Center for Cancer & Cardiovascular Diseases, Japan)

## **Japan Sarcoma Association (JSA)**

Satoshi Teraoka, M.D., Ph.D., Organizer  
(International University of Health and Welfare, Japan)

*The Japan-United States International Workshop  
on The Sarcoma Research and Therapy  
Halekulani, Honolulu, U.S.A.*



**Katsuhito Takahashi, M.D., Ph.D.**

Chief, Department of Molecular  
Medicine and Pathophysiology,  
Sarcoma Specialist,  
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Osaka Medical Center for  
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**Satoshi Teraoka, M.D., Ph.D.**

Board of Directors,  
International University of  
Health and Welfare,  
Tokyo, Japan  
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It is our great pleasure to invite you to “The Japan-United States International Workshop on the Sarcoma Research and Therapy” which will be held on December 4 and 5, 2014 in Honolulu, United States.

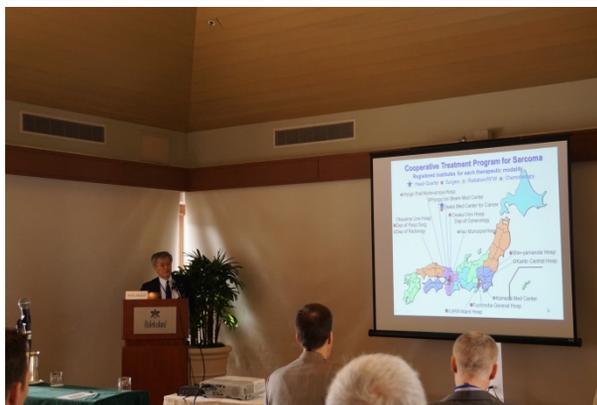
We also announce the foundation of the Japan Sarcoma Association (JSA) which will be organized by diverse memberships including national and international multidisciplinary experts of sarcoma research, diagnosis and therapy (Basic Science, Pathology, Medical Oncology, Abdominal and Thoracic Surgery, Orthopedic Surgery, Gynecology, Urology, Breast Surgery, Pediatrics, Therapeutic and Interventional Radiology), and patients and their families. We placed the Workshop as a Kick-Off Meeting for JSA.

Soft tissue sarcomas constitute 1.5-2% of the malignant solid tumors in Japan, and newly diagnosed cases per year are estimated to be 3000~5000. In both Japan and United States, approximately 60% of soft tissue sarcomas in adult occur in the thoracic, visceral and retroperitoneal/intra-abdominal regions. Those patients with sarcomas, especially in the recurrent and metastatic cases, not covered by orthopedic surgery, were tragically called “cancer refugees” in Japan because coordinated multidisciplinary treatments including surgical, topical and systemic drug therapies have not been established.

Starting from a small group of experts in 2003, with strong supports by patients and families, we established a unique platform for cooperative treatment of sarcoma with “horizontal specialization” by 17 hospitals in which basically each hospital provides the most skillful treatment modality. With this system, in the recent 3 years and 8 months from 2011~2014, total of 627 sarcoma patients were newly enrolled into our cooperative treatment program from more than 300 hospitals in all over Japan, several Asian countries and Hawaii. Surgical treatment group in the abdominal and thoracic surgery performed 380 operations, and topical treatment group in the gastrointestinal medicine performed 180 radiofrequency ablation for liver metastasis. Medical oncology group treated 169 cases with pazopanib molecular-targeted therapy.

In this Workshop, each of the best experts of our cooperative sarcoma treatment program in Japan as well as interactive sarcoma experts in the United States will give an exciting talk on their skillful experiences and the “Up-To-Date” advances in both basic and clinical sciences of sarcoma.

# Photo galleries (1)



*Thursday, December 4, 2014*

**10:00-12:00 (Hau Terrace)**

# **Frontiers in the Genomic Landscape and Histogenesis of Sarcoma**

Moderators

Katsuhito Takahashi

(Osaka Medical Center for Cancer & Cardiovascular Diseases, Japan)

Robin L. Jones

(Washington University, U.S.A.)

*The Japan-United States International Workshop  
on The Sarcoma Research and Therapy  
Halekulani, Honolulu, U.S.A.*



**Andrew Brohl, M.D.**  
 Oncogenomics Section, Pediatric  
 Oncology Branch,  
 Center for Cancer Research,  
 National Cancer Institute,  
 Department of Genetics and  
 Genomic Sciences.  
 Icahn School of Medicine at  
 Mount Sinai, New York, U.S.A  
 andrew.brohl@mssm.edu

**Javed Khan, M.D.**  
 Deputy Chief and Head,  
 Oncogenomics Section  
 Center for Cancer Research,  
 National Cancer Institute,  
 Bethesda, U.S.A.

## Whole genome analysis of Ewing's sarcoma

Andrew S Brohl<sup>ab</sup>, David A. Solomon<sup>c</sup>, Wendy Chang<sup>a</sup>, Jianjun Wang<sup>a</sup>, Young Song<sup>a</sup>, Sivasish Sindiri<sup>a</sup>, Rajesh Patidar<sup>a</sup>, Laura Hurd<sup>a</sup>, Li Chen<sup>a</sup>, Jack F Shern<sup>a</sup>, Hongling Liao<sup>a</sup>, Xinyu Wen<sup>a</sup>, Julia Gerard<sup>h</sup>, Jung-Sik Kim<sup>h</sup>, Jose Antonio Lopez Guerrero<sup>d</sup>, Isidro Machado<sup>d</sup>, Daniel H. Wai<sup>e</sup>, Piero Picci<sup>f</sup>, Timothy Triche<sup>e</sup>, Andrew E. Horvai<sup>c</sup>, Markku Miettinen<sup>g</sup>, Jun S Wei<sup>a</sup>, Daniel Catchpool<sup>h</sup>, Antonio Llombart-Bosch<sup>d</sup>, Todd Waldman<sup>i</sup>, & Javed Khan<sup>a</sup>

<sup>a</sup>Oncogenomics Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health. Bethesda, MD 20892

<sup>b</sup>Department of Genetics and Genomic Sciences. Icahn School of Medicine at Mount Sinai, New York, NY 10029

<sup>c</sup>Department of Pathology, University of California, San Francisco, San Francisco, CA 94143

<sup>d</sup>Department of Pathology, University of Valencia, Valencia, Spain

<sup>e</sup>Center for Personalized Medicine, Children's Hospital Los Angeles, University of Southern California Los Angeles, Los Angeles, CA

<sup>f</sup>Laboratory of Experimental Oncology, Rizzoli Institute, Bologna, Italy

<sup>g</sup>Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892

<sup>h</sup>The Tumour Bank, The Children's Cancer Research Unit, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

<sup>i</sup>Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine, Washington, DC 20057

**Background and Aims:** The Ewing sarcoma family of tumors (EFT) is a group of highly malignant small round blue cell tumors occurring in children and young adults. We report here one of the first and largest genomic analyses to date of 101 EFT (65 tumors and 36 cell lines).

**Methods:** We utilize a combination of whole genome sequencing, RNA sequencing and targeted sequencing approaches.

**Results:** We discover that EFT has a very low mutational burden (0.15 mutations/Mb) but frequent deleterious mutations in the cohesin complex subunit *STAG2* (21.5% tumors, 44.4% cell lines), homozygous deletion of *CDKN2A* (13.8% and 50%) and mutations of *TP53* (6.2% and 71.9%). Using whole transcriptome sequencing, we find that 11% of tumors pathologically diagnosed as EFT lack a typical *EWSR1* fusion oncogene and that these tumors do not have a characteristic Ewing sarcoma gene expression signature. We identify samples harboring novel fusion genes including *FUS-NCATc2* and *CIC-FOXO4* that may represent distinct small round blue cell tumor variants. In an independent EFT tissue microarray cohort, we show that *STAG2* loss as detected by immunohistochemistry may be associated with more advanced disease ( $p=0.15$ ) and a modest decrease in overall survival ( $p=0.10$ ).

**Discussion:** We discover that Ewing sarcomas despite having a low mutational burden are frequently affected by mutations in *STAG2*. We show that Ewing sarcoma patients whose tumors exhibit *STAG2* loss may have a worse prognosis. Additionally, we identify a subset of tumors that were diagnosed as Ewing sarcoma that appear to be distinct from the majority based on genetic and molecular characteristics.

**Summary:** Our results significantly advance our understanding of the genomic and molecular underpinnings of Ewing sarcoma and provide a foundation towards further efforts to improve diagnosis, prognosis, and precision therapeutics testing.



**Takuro Nakamura, M.D., Ph.D.**  
Chief, Division of Carcinogenesis,  
The Cancer Institute,  
Japanese Foundation for Cancer Research,  
Tokyo, Japan  
takuro-ind@umin.net

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## **Histogenesis of Ewings' sarcoma: Modeling fusion gene-associated bone and soft tissue sarcoma**

Takuro Nakamura

Division of Carcinogenesis, The Cancer Institute, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan  
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Generation of animal models for human sarcoma is important not only for understanding the carcinogenic mechanisms but also for utilizing the models as ideal platforms for innovative therapies. However, it is often difficult to establish the models by introducing sarcoma-associated fusion genes when its cell-of-origin is unknown. Appropriate cellular context modulated by the epigenetic status is an important factor for the function of fusion genes. We have established a mouse model for Ewing's sarcoma (ES), synovial sarcoma (SS) and alveolar soft part sarcoma (ASPS) by introducing their specific fusion genes (*EWS-FLI1*, *SYT-SSX1* or *ASPL-TFE3*) into embryonic mesenchymal cells. Using microdissection and immunoselection by anti-PTHLH, *EWS-FLI1* expression in murine embryonic cells invariably induced ES-like small round cell sarcoma. We could clarify that the cell-of-origin of ES is highly enriched in the embryonic superficial zone (eSZ) of embryonic long bone that contains osteochondrogenic progenitors abundantly. *EWS-FLI1* downstream genes were quite active in eSZ cells, where the chromatin structure of the *FLI1*-responsive loci was open.

Retrovirus-mediated gene transfer of *SYT-SSX1* into murine embryonic mesenchymal cells also resulted in both monophasic and biphasic SS. Candidate cooperative genes for *SYT-SSX1* were isolated from common retroviral integration sites by retrovirus tagging in SS. Co-expression experiments revealed that a certain microRNA indeed cooperates with *SYT-SSX1* in sarcomagenesis. Increased vasculogenesis and the high metastatic activity, typical features of human ASPS, as well as a characteristic morphological pattern were obtained by *ASPL-TFE3* expression in embryonic mesenchymal cells. Thus, relationship between fusion genes and cell-of-origin is important for sarcoma development, and the methods provide preclinical animal models of human sarcoma valuable for evaluating novel therapies.

## Photo galleries (2)



*Thursday, December 4, 2014*

**12:00-14:00 (Garden Terrace)**

# **Luncheon Seminar**

## **Clinical evaluation and treatment of leiomyosarcoma**

Moderators

Hiroyuki Narahara

(Hyogo Prefectural Nishinomiya Hospital, Japan)

*The Japan-United States International Workshop  
on The Sarcoma Research and Therapy  
Halekulani, Honolulu, U.S.A.*



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## Clinical evaluation and treatment of leiomyosarcoma

Katsuhito Takahashi<sup>1</sup>, Hisako Yamamura<sup>1</sup>, Yukihiro Koike<sup>2</sup>, Hiroyuki Narahara<sup>3</sup>, Yu Ooyama<sup>4</sup>, Shin-ichi Toyooka<sup>5</sup>, Ryo Hatae<sup>6</sup>, Yasuo Ono<sup>6</sup>, Jun Yashima<sup>7</sup>, Satoshi Teraoka<sup>7</sup>

<sup>1</sup>Department of Molecular Medicine and Pathophysiology, Osaka Medical Center for Cancer and Cardiovascular Diseases. <sup>2</sup>Department of Gastrointestinal Medicine, Kanto Central Hospital. <sup>3</sup>Department of Medical Oncology, Hyogo Prefectural Nishinomiya Hospital. <sup>4</sup>Department of Medical Oncology, Kameda Medical Center. <sup>5</sup>Department of Thoracic Surgery, Okayama University Hospital. <sup>6</sup>Department of Surgery, Fuchinobe General Hospital, Shin-Yamanote Hospital. <sup>7</sup>Department of Transplantation Surgery, International University of Health and Welfare, Atami Hospital

**Background and Aims:** Soft tissue sarcomas in adult are rare and essentially incurable malignancies, especially in the recurrent and metastatic cases. They constitute approximately 1.5~2% of the total patients with malignant solid tumors in adult and newly-diagnosed cases per year are estimated to be 3000~5000 in Japan. Leiomyosarcoma is originated from smooth muscle cells in everywhere in the body and the most abundant sarcoma in the thoracic, visceral, retroperitoneal and intra-abdominal regions in adults. To overcome the difficulties in medical treatment of those sarcoma patients, we need both a novel platform of treatment and novel treatment modalities. **Materials and Methods:** We constructed a unique platform for “horizontal” cooperation among 17 hospitals, essentially giving the most skillful one treatment modality by one group (hospital), reminiscent of so-called “horizontal specification” in a business model of electronic devices. The alliance enables the patients-intensive care and development of our strong experiences on the rare malignancies. **Results:** To summarize the results from 2011 to 2013 and August in 2014, total of 627 primary or recurrent sarcoma cases, including 284 cases of leiomyosarcoma were newly enrolled in our cooperative treatment program, and 1944 follow-up cases were visited our hospital. Surgically resected or biopsied sarcoma tissues were analyzed by immunohistochemistry, genomic sequencing of mutations in the disease-responsible genes and cell cultures. Treatment modalities applied were 381 cases for surgical treatment (4 hospitals), 180 cases for radiofrequency ablation therapy of liver metastasis (1 hospital) and 169 cases for pazopanib anti-angiogenesis molecular-targeted therapy (6 hospitals). Down-regulation and loss of VEGFR2 (Flk-1) expression in the tumor vasculature were significantly correlated to the lack of effectiveness of pazopanib treatment. There was a tendency that leiomyosarcoma with highly differentiated properties showed more hypoxic natures with many tumor vasculature with reduced VEGFR2 expression. **Discussion and Summary:** We successfully developed a unique platform for cooperative medical treatment of patients with sarcoma which enabled, for the first time to our knowledge, patients-intensive care and raised our clinical skills and knowledge on the rare malignancies. With the abundant cases on our platform, we will launch whole genome and exome analyses of 200 patients with leiomyosarcoma.

## Photo galleries (3)



## Photo galleries (4)



*Thursday, December 4, 2014*

**14:00-15:20 (Hau Terrace)**

# **Frontiers in the Surgical Oncology in Sarcoma**

Moderators

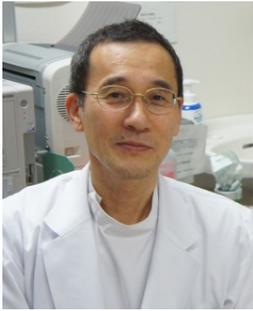
Robert Maki

(Mount Sinai Hospital, U.S.A.)

Jun Yashima

(International University of Health and Welfare, Atami Hospital,  
Japan)

*The Japan-United States International Workshop  
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## **Challenging surgical treatment of abdominal, retroperitoneal and gastrointestinal sarcoma**

Yasuo Ono<sup>1,2</sup>, Shinichi Kuroyama<sup>1</sup>, Ryo Hatae<sup>2</sup>, Syoji Maruyama<sup>2</sup>,  
Jun Yashima<sup>3</sup>, Hiroyuki Shirai<sup>3</sup>, Satoshi Teraoka<sup>3</sup>

<sup>1</sup>Department of Surgery, Fuchinobe General Hospital

<sup>2</sup>Department of Gastrointestinal Surgery, Shin-yamanote Hospital

<sup>3</sup>Department of Transplantation Surgery, International University of Health and Welfare, Atami Hospital

**Background and Aims:** Surgical treatment for soft tissue sarcomas has very difficult problems, especially in patients with recurrent tumors in thoraco-abdominal cavities.

**Methods and Results:** From January 2009 to December 2013, we experienced over 400 operations for soft tissue sarcomas on the platform of our cooperative treatment program. Most of our cases are recurrent diseases although there are few primary cases. We report here our experiences and some operative cases, and try to clarify some important notes on surgical treatment of soft tissue sarcomas in the abdominal, retroperitoneal and gastrointestinal regions.

**Discussion:** In primary localized cases, we are convinced that complete operative resection is the best modality for cure. But after initial therapy, many patients with soft tissue sarcomas have local recurrence and distant metastasis because the tumor progression and disease stage are so advanced and tumor size is very large when they are diagnosed. On the treatment of recurrent cases, what modality should be chosen is controversial and aggressive operation has not been easily acceptable. But in some cases of our experiences, operation did prolonged their survival and thus was highly effective and considered modality for local control even in the recurrent and metastatic cases.

**Conclusion:** We have achieved patients-intensive surgical treatment for soft tissue sarcomas in the abdominal, retroperitoneal and gastrointestinal regions where most of the recurrent cases have not been received systematic surgical treatment in Japan. With our experiences on both successful and unsuccessful cases, we feel that surgical treatment could be a treatment modality to be considered. Undoubtedly, in both clinical and biological aspects, it is important to know the conditions and indications for surgical treatment of patients with recurrent and metastatic soft tissue sarcomas in the thoraco-abdominal regions.



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Department of Thoracic Surgery  
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## **Surgical treatment of multiple lung metastasis of sarcoma**

Shinichi Toyooka, Hiromasa Yamamoto, Junichi Soh, Kentaroh Miyoshi,  
Seiichiro Sugimoto, Masaomi Yamane, Takahiro Oto, Shinichiro Miyoshi  
Department of Thoracic Surgery, Okayama University Hospital, Okayama, Japan

**Background and Aims:** Sarcoma is one of aggressive malignant tumors, which often metastasises to the lung with multiple lesions. While systematic therapies are principally treatments of first choice for patients with metastatic lung tumors, effective systemic treatments have not been established yet for many kinds of sarcomas. Surgical resection for metastatic lung tumors is a strong treatment to control local disease although it is not a curative therapy. Thus, its indication should be carefully determined.

**Methods and Results:** Our selection criteria to perform pulmonary resection for metastatic sarcoma is that 1) performance status should not be deteriorated or impaired with surgery, 2) life-threatening lesions need to be removed, 3) other lesions except lung can be managed, 4) molecular characterization of tumors can be useful information for determination of systematic therapy. Considering these, pulmonary resection is mainly a bridge to the subsequent treatment. Based on the above-mentioned criteria, we performed pulmonary resection in 97 consecutive sarcoma patients with pulmonary metastasis between 2011 and 2014 (as of October 27th, 2014). A total of 167 procedures were performed. The procedure consisted of 132 partial resections, 22 segmentectomies with or without partial resections, 12 lobectomies with or without partial resections, and 1 basal segmental auto-transplantation after pneumonectomy. We resected 693 tumors and the average number of tumors per surgery was 4.1. All the patients discharged from our hospital on foot, suggesting that our strategy including procedure is feasible.

**Discussion and Summary:** As future perspective, it is important to determine a new indication for surgery based on evidence to select patients who maximally benefit from surgical resection. We will discuss about our experienced cases on this viewpoint.



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## **The Surgical Management and Potential for Immunotherapy in Retroperitoneal Liposarcoma**

William W. Tseng<sup>1\*</sup>, Raphael E. Pollock<sup>2\*</sup>

<sup>1</sup>Department of Surgery, Section of Surgical Oncology, Keck School of Medicine, University of Southern California, Los Angeles, CA and the Hoag Family Cancer Institute, Hoag Memorial Hospital Presbyterian, Newport Beach, CA

<sup>2</sup>The James Comprehensive Cancer Center, Ohio State University, Columbus, OH

\*previously at The University of Texas M.D. Anderson Cancer Center, Houston, TX

**Background and Aims:** Surgery offers the only chance for cure in well-differentiated (WD) and dedifferentiated (DD) retroperitoneal liposarcoma. Unfortunately, surgery is often challenging and locoregional recurrence occurs frequently. Radiation therapy and chemotherapy are not effective. Our aims were 1) to characterize the patterns of locoregional recurrence to help guide the extent of surgery and 2) to explore the potential for immunotherapy in this disease.

**Methods:** Tumor number and location(s) at initial presentation for surgery and at recurrence were analyzed from a large, single institution clinical database. In separate experiments, fresh tumor specimens from surgery were processed to isolate tumor-infiltrating lymphocytes (TILs). Expression of surface markers on TILs was assessed by flow cytometry and the intratumoral location of the immune cells was determined by immunohistochemistry.

**Results:** Multifocal disease is common in WD / DD retroperitoneal liposarcoma, including the development of tumors at remote, locoregional sites (“outside field”). In patients with initial unifocal disease, no clinicopathologic or treatment-related variables could predict multifocal or outside field progression, including the type or extent of surgery. Liposarcoma tumors contain CD8-positive, cytotoxic T cells with a high frequency of PD-1 expression. In addition, immune cells can form intratumoral lymphoid structures that are reminiscent of primitive lymph nodes.

**Discussion and Summary:** The aggressiveness of surgery in WD / DD retroperitoneal liposarcoma should be individualized to each patient with consideration of distinct patterns of locoregional recurrence. Immune cells, including cytotoxic CD8 T cells, are found naturally in these tumors. The existence of an adaptive immune response and the effectiveness of immunotherapy, including anti-PD-1 agents, deserve further investigation.

## Photo galleries (5)



*Thursday, December 4, 2014*

**16:00-18:00 (Hau Terrace)**

# **Leading and Pioneering Topical Treatment of Sarcoma**

Moderators

Yu Oyama

(Kameda General Hospital, Japan)

Ryo Hatae

(Shin-yamanote Hospital, Japan)

*The Japan-United States International Workshop  
on The Sarcoma Research and Therapy  
Halekulani, Honolulu, U.S.A.*



Yukihiro Koike, M.D., Ph.D.

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## Radio-frequency ablation therapy for multiple hepatic metastases of sarcoma

Yukihiro Koike

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**Background:** The liver is the most common site of metastases from sarcoma. At present, surgery is considered to be the only therapy that offers the possibility of cure for patients with hepatic metastatic diseases. However, there are not many patients with the metastases treatable by the surgical resection, while the remainings are treated with chemotherapy or best supportive care. This study was conducted to clarify the safety and efficacy of percutaneous radiofrequency ablation (RFA) for unresectable liver metastases of sarcoma.

**Methods:** From 2004 to 2008, 59 patients with unresectable liver metastases from sarcoma were treated by RFA, regardless of extent of hepatic metastases or presence of extrahepatic lesions. At the initial ablation, the mean number and size of hepatic tumor foci were  $6.9 \pm 7.6$  (mean  $\pm$  SD, range 1-30) and  $48 \pm 34$  mm (mean  $\pm$  SD, range; 11-142 mm), respectively. 46 patients have extrahepatic metastases. 51 patients were nonresponders to previous chemotherapy. Prognostic factors of the patients were evaluated by univariate and multivariate Cox proportional hazard model.

**Results;** Until Oct. 2008, the enrolled 59 patients have received a total of 164 RFA procedures. There was no procedure-related mortality. Six complications (3.3%; 3 intra-abdominal hemorrhage, 1 liver abscess, 1 cholangitis) were observed. At the initial ablation, all the patients enjoyed the benefit of RFA (= or more 80% of the liver metastases were destroyed). 1-, 2-year survival rates after RFA were 86 % and 68 %, respectively. Multivariate analysis showed that prior chemotherapy, no factors were significant prognostic factors.

**Conclusion;** This study showed RFA could safely reduce the volume of hepatic metastases, and might improve the prognosis of patients with unresectable liver metastases from sarcoma.



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Kameda Medical Center  
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## Cryoablation therapy for multiple lung metastases of sarcoma: Twelve years-experience of percutaneous cryoablation for lung tumors

Hiroaki Nomori

Departments of Thoracic Surgery, Kameda General Hospital, Kameda Medical Center, Chiba, Japan

**Background and Aims:** Cryoablation for lung tumors had been conducted by the device using argon gas from 2002 to 2012, and by using liquid nitrogen since 2013. The results of the basic experiments and clinical applications are presented.

**Materials and Methods:** From 2002 to 2012, by the device using argon gas, 193 patients with 238 lung tumors (22 primary lung cancers and 216 metastatic lung cancers) were treated. Since 2013, 27 patients with 32 lung tumors have been treated by the device using liquid nitrogen. Before starting the cryoablation by using liquid nitrogen, the size and temperature of the frozen area (i.e., iceball) in gel and pig lung were measured.

**Results:** By using the device using argon gas (from 2002 to 2012), the 3 years-local control rate for metastatic colon cancers were 80% for tumors less than 1.5 cm and 29% for those larger than 1.5 cm. For 22 patients with inoperable stage I non-small cell lung cancer, local control rate and overall survival at 3 years were 97% and 88%, respectively. The major complication was pneumothorax which required chest tube drainage (18%). The results of basic experiments and clinical application by using liquid nitrogen were as follows: (1) In the pig lung, the 2.4D and 3.4D probes made the iceball 5.2 and 5.5 cm in diameter after 4 freeze/thaw cycles, respectively, and the temperatures at a radial distance of 1.5 cm from the 2.4D and 3.4D probes reached  $-49^{\circ}$  C and  $-58^{\circ}$  C after the 4 cycles, respectively, which were not only cold enough for cytotoxic temperature ( $-20^{\circ}$  C) but also were more powerful than the device using argon gas; (2) In clinical application, the ablation area was  $3.0 \pm 1.8$  times larger than the maximal tumor size. Ten of the 27 patients (37%) suffered pneumothorax that required chest tube drainage for a few days. There were no other major complications.

**Discussion and Summary:** Cryoablation for lung tumors is feasible with regard to local control, survival, and complication. The cryoablation by using liquid nitrogen would be more powerful than that using argon gas.



**Yusuke Demizu, M.D.**

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Hyogo Ion Beam Medical Center,  
Hyogo, Japan  
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## **Particle radiotherapy (carbon ions and protons) for sarcoma**

Yusuke Demizu

Department of Radiology, Hyogo Ion Beam Medical Center, Hyogo, Japan

Particle therapy is a type of radiotherapy. While photons are used for conventional radiotherapy, beams with completely different characteristics such as carbon ions and protons are employed for particle therapy. Particle therapies that use carbon ions and protons are generally described as carbon ion therapy (CIT) and proton therapy (PT), respectively.

Photons exert maximum energy near the body surface; this energy gradually decreases and passes through the entire thicknesses of the body structures. In contrast, charged particles show relatively low energy doses near the body surface and deposit maximum energy immediately before halting deep within the body (called the Bragg peak). By modifying this peak according to the tumor position and size (spread-out Bragg peak), charged particles can be used to deliver high-dose radiation to the tumor while minimizing the doses delivered to the organs at risk.

Carbon ions are likely to induce DNA double-strand breaks that are difficult to be repaired and can lead to cell death. Therefore, carbon ions possess the following biological characteristics and are expected to be effective even for photon-resistant tumors: a high relative biological effectiveness, with biological effects 1.2–3.5-fold greater than those obtained with equal physical photon doses; a low oxygen enhance ratio, which will be effective against photon-resistant hypoxic cells; and a low dependency on the cell cycle, which will be effective against photon-resistant late-S-phase cells. Meanwhile, the biological effects of protons are considered to be nearly identical to those of photons.

The mainstay of definitive treatment for sarcoma has been resection. For unresectable or incompletely resected cases, radiotherapy can be a treatment option; however, sarcoma is considered to be resistant to photon radiotherapy, and particle therapy such as CIT and PT has shown better results.

In this presentation, I will talk about the current clinical outcomes of particle therapy for sarcoma.

## Photo galleries (6)



*Thursday, December 4, 2014*

**18:00-18:45 (Hau Terrace)**

# **Poster Presentation Patient Advocacy**

Moderators

Yasuo Ono

(Fuchinobe General Hospital, Japan)

Hisako Yamamura

(Osaka Medical Center for Cancer and Cardiovascular Diseases,  
Japan)

*The Japan-United States International Workshop  
on The Sarcoma Research and Therapy  
Halekulani, Honolulu, U.S.A.*



Cranmer Lee, M.D., Ph.D.

Associate Professor, Sarcoma Oncology Clinic,  
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## Neoadjuvant Chemoradiotherapy (nCRT) in the Management of Soft Tissue Sarcomas (STS): The University of Arizona Experience

Lee D. Cranmer<sup>1</sup>, Patti E. Dexter R.N., Krisha Howell<sup>2</sup>, Matthew Seidel<sup>3</sup>, James Warneke<sup>4</sup>  
Sarcoma Oncology Clinic, Department of Medicine<sup>1</sup>, Radiation Oncology<sup>2</sup>, Orthopedic Surgery<sup>3</sup>,  
and Surgery<sup>4</sup>, University of Arizona Cancer Center, Tucson, Arizona, USA

**Background:** Patients with large, high-grade STS are at risk of both local and distant recurrence. Strategies combining surgery and radiotherapy (RT) generally yield excellent local control, but some patients have tumors that are difficult to excise completely. Neoadjuvant combination chemoradiotherapy (nCRT) may improve local control and treat pre-existing micrometastatic disease. Combination ifosfamide and etoposide (IE) has long been administered concurrently with radiation therapy in the pediatric oncology setting. We evaluated our results of administration of this nCRT regimen for STS patients.

**Methods:** Eligible STS patients were at least 18 yo treated with neoadjuvant or adjuvant RT for primary disease. All had deep tumors classified as high-grade. The exploratory group of patients had received nCRT with IE. The controls consisted of patients receiving treatment for large (>5cm), high-grade STS with surgery and either neoadjuvant or adjuvant RT (“RT”). Data regarding demographics, baseline characteristics, treatment outcomes and survival were abstracted. Metastasis-free and overall survival were analyzed using univariate Cox proportional hazards.

**Results:** 27 eligible patients were identified (13 nCRT, 14RT). Neither gender proportions (12 F, 15 M), age at diagnosis (median 59y, range 22-88), primary location (15 extremity vs. 12 trunk/internal), nor primary tumor size differed between the groups. Follow-up time was significantly shorter in the group receiving nCRT (median 25m vs. 43m for RT,  $p=0.03$ ). nCRT patients received lower total radiation doses (median 5000 cGy vs. 5520 cGy for RT,  $p=0.008$ ). Local recurrences were uncommon (2/13 nCRT vs. 2/14 RT,  $p=ns$ ). Metastases developed in 3/12 nCRT (one excluded due to unresectable disease at presentation) vs. 6/14 RT; 3/12 nCRT died vs. 6/14 RT. In Cox analyses, nCRT was associated with a statistically non-significant decreased risk of metastasis development (HR=0.64,  $p=0.51$ ) and death (HR=0.49,  $p=0.34$ ). Positive margins at definitive surgery were associated with an increased risk of metastasis (HR=2.83,  $p=0.14$ ) and death (HR=2.00,  $p=0.31$ ). Gender, age at initial diagnosis, radiation dose and tumor size were not associated with metastasis-free or overall survival.

**Conclusions:** Combination surgery and radiation therapy yields excellent local control of large, high-grade STS. Our data were unable to demonstrate a statistically significant impact of nCRT on metastasis-free or overall survival. However, the estimated hazard ratios (0.64 and 0.49, respectively) do not contradict the hypothesis of possible benefit from nCRT versus RT. More complex nCRT regimens are undergoing evaluation, but the relative simplicity of the IE regimen, and its non-use of an anthracycline, make this regimen attractive. Further evaluation of IE-based nCRT may be worthwhile.

**Limitations:** This is a relatively small study, limiting its statistical power. Further, it is a single-center retrospective study, which may introduce unappreciated biases. The follow-up duration is longer for RT vs. nCRT. This could provide an alternate explanation for the observed hazard ratios, with further follow-up leading the metastasis-free and overall survival rates to coincide.



**Robin L. Jones, M.D., MRCP**

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Fred Hutchinson Cancer Research Center  
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## **The effect of pazopanib prior to preoperative chemotherapy for patients with extremity soft tissue sarcoma: A randomized trial to evaluate response by imaging**

Robin L Jones<sup>1</sup>, Seth M Pollack<sup>1</sup>, Darin Davidson<sup>1</sup>, Erica Peters<sup>1</sup>, Rosa Yeh<sup>1</sup>, Elizabeth Loggers<sup>1</sup>, Edward Kim<sup>1</sup>, Ernest Conrad<sup>1</sup>, Chris W Ryan<sup>2</sup>, Janet Eary<sup>3</sup>, Eve Rodler<sup>1</sup>

<sup>1</sup>Medical Oncology, University of Washington/ Fred Hutchinson Cancer Research Center; <sup>2</sup>Medical Oncology, Oregon Health Sciences University, Portland; <sup>3</sup>Radiology, University of Alabama, Birmingham

**Background and Aims:** Soft tissue sarcomas are heterogeneous, rare group of mesenchymal malignancies. Despite adequate surgical resection and radiation, approximately 50% of patients will die of metastatic disease. Numerous trials have failed to show a conclusive survival benefit for pre-/ post-operative chemotherapy. Consequently there is an unmet need for novel therapies in the setting of localized disease. Pazopanib has been approved for the treatment of metastatic soft tissue sarcoma. This is a pilot trial assessing the value of pazopanib prior to pre-operative chemotherapy using PET as a marker of response.

**Methods:** Patients with extremity or chest wall soft tissue sarcomas greater than 5 cm are eligible for trial entry. Patients with grade 2 or 3 tumors with adequate hematological, renal and liver function will be entered. Patients will be randomized 2: 1 to pazopanib or placebo during the run-in window prior to commencing therapy. Patients who respond to pazopanib will have the option to continue pazopanib for one year following surgery. The trial outline is shown in Figure 1.

The primary aim of the trial is to determine the absolute values and changes in standardized uptake value (SUV) by FDG-PET before and after a 14 day run in period of pazopanib or placebo and to compare this to the change in SUV following pre-operative chemotherapy. Another objective will be to evaluate the correlation between anti-angiogenic activity and pazopanib drug exposure and to assess the response rate by RECIST after the 14 day run-in period and compare this to the response rate following pre-operative chemotherapy. Secondary objectives include the evaluation of the activity of pazopanib with pre-operative chemotherapy as measured by histological necrosis at surgery and the change in putative plasma and tumor biomarkers of angiogenesis. A further secondary aim will be to evaluate the safety of sequential pazopanib and pre-operative chemotherapy.

**Results:** Recruitment is ongoing, with 11 randomized patients. Updated results will be presented at the meeting.



**Ryo Hatae, M.D.**

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## **Role of surgery in the treatment of soft tissue sarcoma in the thoraco-abdominal regions**

Ryo Hatae

Department of Gastrointestinal Surgery, Shin-Yamanote Hospital, Tokyo, Japan

We have expertised surgical treatment in the platform of cooperative treatment of soft tissue sarcoma, so called Cure Sarcoma Board. In the last 5 years, we have experienced over 350 operations in patients with abdominal, thoracic and retroperitoneal sarcoma, most of the cases are recurrence.

Currently, there was no EBM which shows effectiveness of surgical treatment for recurrent soft tissue sarcoma because it was impossible to carry out the patient-intensive studies. In general, systemic chemotherapy and molecular-targeted therapy has been considered for treatment of the patients with recurrent or metastatic sarcoma. However, in the clinical settings, their effectiveness is not sufficient. It is not known whether we can get better prognosis if we combine local therapy such as surgery and systemic therapy in the recurrent cases. To achieve better prognosis we are trying to do multi-disciplinary treatments, including systemic chemotherapy and molecular-targeted therapy, radiation therapy and surgical operation.

Although it is difficult to prove the efficacy of surgical therapy in the recurrent soft tissue sarcomas in the abdominal, retroperitoneal and gastrointestinal regions, we present here our current experiences and outcomes of surgical treatment of recurrent and metastatic soft tissue sarcomas in the thoraco-abdominal regions and discuss the indications and conditions for this potentially important treatment modality.



**Jun Yashima, M.D.**

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## **Outcome of surgical resection for intra-abdominal and retroperitoneal soft tissue sarcomas**

Jun Yashima<sup>1</sup>, Hiroyuki Shirai<sup>1</sup>, Yasuo Ono<sup>2</sup>, Satoshi Teraoka<sup>1</sup>.

<sup>1</sup>Atami hospital, International University of Health and Welfare, Shizuoka, Japan.

<sup>2</sup>Fuchinobe general hospital , Kanagawa, Japan.

**Background and Aimes:** Surgical resection is considered the standard treatment for intra-abdominal and retroperitoneal soft tissue sarcoma(IARS) .We here report the outcome of surgical resection for IARS at IUHW Atami hospital, Japan.

**Materials and Methods:** A total of 60 patients underwent 107 surgical resections for IARS between 2010 and 2014. Deta on primary and recurrent tumor were collected including staging, histopathological diagnosis, operative procedures, postoperative complications, and perioperative mortality, as well as 3-years survival.

**Results:** Histopathologically, 10 different types of IARS were found in the cases. The 3-years survival rate for overall patients is approximately 40%. Patients with liposarcoma, or primary cases were tended to have better prognosis. Total pelvic exenteration was indicated in 7cases, and femoro-femoral bypass was needed in 4 cases.

**Discussion and Summary:** The mortality in our center is not satisfactory, possibly because the majority of the patients had far-advanced stage disease. Further improvement of the outcome may require other adjuvant therapy, such as chemotherapy, molecular-targeted therapy and/or radiotherapy.



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## **Surgical treatment for metastatic lung tumors from various sarcomas: a single institutional experience**

Hiromasa Yamamoto, Shinichi Toyooka, Junichi Soh, Kentaroh Miyoshi, Seiichiro Sugimoto, Masaomi Yamane, Takahiro Oto, and Shinichiro Miyoshi

Department of Thoracic Surgery, Okayama University Hospital, Okayama, Japan

**Background and Aims:** Sarcoma is one of the refractory malignant tumors and often develops pulmonary metastasis. Systemic treatment such as chemotherapy should be appropriate for patients with metastatic lung tumors. However, effectiveness of the chemotherapeutic or molecular-targeted drugs are yet to be sufficient and thus surgical resection is a therapeutic option for metastatic lung tumors so as to control the disease progression.

**Methods and Results:** Between January 2011 and October 2014, we had 97 consecutive sarcoma patients who underwent pulmonary metastasectomy in Okayama University Hospital. A total of 167 pulmonary metastasectomies were performed and 693 metastatic nodules were resected. Average number of tumors per intervention was 4.1 (range 1-19). These sarcoma patients consisted of 25 males and 72 females, and their average age was 53.3 years (range 14-80 years). Leiomyosarcoma was the most common histological subtype ( $n = 57$ , 58.8%) and uterus was the most common location of the primary disease. Operative procedures were composed of 132 partial resections, 22 segmentectomies with or without partial resections, 12 lobectomies with or without partial resections, and 1 basal segmental auto-transplantation after pneumonectomy. The postoperative complications were limited, showing that pulmonary metastasectomies for sarcomas are acceptable.

**Conclusions:** It is necessary to develop the evidence for performing surgical resections only for the patients who receive the benefit of it.



Kayo Yasuda, M.D.

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Hyogo, Japan

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## Combination chemotherapy of Pazopanib and Denosumab for soft tissue sarcoma with bone metastases

Department of Gastroenterology, Hyogo Prefectural Nishinomiya Hospital, Hyogo, Japan

Kayo Yasuda, Hiroyuki Narahara, Yuichi Yasunaga, Yoshiaki Inui, Sumio Kawata

**Background and Aims:** We conducted a retrospective analysis on combination chemotherapy of pazopanib and denosumab for soft tissue sarcoma (STS) with bone metastases.

**Methods:** In this study, the patients with metastatic STS treated with both pazopanib and denosumab from November 2012 till June 2014, consecutively, were retrospectively analyzed.

**Results:** Twenty patients (15 leiomyosarcomas, 5 other subtypes) with multiple bone metastases were identified. Median age was 60 years old (range 37-81) and 16 females and 4 males were included. The primary organ was identified as the uterus in 9 patients, the retroperitoneum in 5 patients and others in 6 patients. Nine patients were in the second or later line setting and 11 patients were in the first-line setting. All the patients included were evaluable by RECIST 1.1, and 13 patients were evaluated as PR/SD (Disease Control Rate: 65%) but 7 patients showed PD. Median OS is still not-reached and median PFS was 2.6 months. No skeletal related events were observed in this series.

**Conclusions:** The combination therapy of pazopanib with denosumab is promising and further investigations are warranted. It is suggested that this chemotherapy supports synergistic effect between these two drugs in STS.



**Sumito Nishidate**

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## **Patient Advocacy for Gastrointestinal Stromal Tumor (GIST)**

Sumito Nishidate Kimie Sakurai Yoshihiro Takanashi

Specified Nonprofit Organization (NPO) "GISTERS"

Clean Center Bldg., 5th Flr.

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Kanagawa, 231-0062, Japan

Homepage : <http://www.gisters.info/>

e-mail : [mail@gisters.info](mailto:mail@gisters.info)

We are expanding information-sharing network of GIST/Sarcoma patients for 10 years.

Creating the social networking site "GISTERS.net" in 2008, many people joined us from whole country and current number of our membership is more than 550.

The "GISTERS.net" aims to be a research platform that advances treatment information like PatientsLikeMe. With support of "Japanese Study Group On GIST" and "The Research Group for Rare Neoplasms of Japan:Gran-Japan", we hold GIST Study meeting every year in each place since 2010, gaining knowledge of GIST epidemiology and the latest treatment methodology.

Established the non profit organization in 2013, we submit demanding paper for the early approval of the medicine. A doctor-led clinical trial of Stivarga was carried out before approval which was the first drug for compassionate use in Japan.

From here on, we will strengthen a relationship between our members and specialist for various parts of the country, promote activities to share information with large amount of patient families who does not access to the internet, progress GIST treatment united with medical staff.



## Hiroyuki Onishi

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## Patient Advocacy for Sarcoma: The Activity of "CureSarcoma"

Hiroyuki Onishi, Tadahito Ito, Yoichi Shizuku, Ryo Inoue, Etsuko Masuda

NPO Curesarcoma

#B, 1-33-7 Sanno, Ota-ku, Tokyo 143-0023, Japan

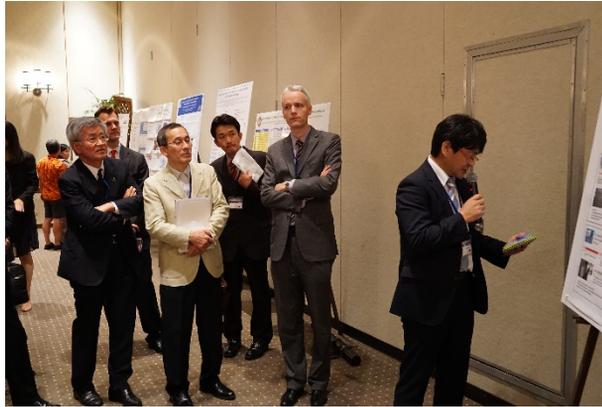
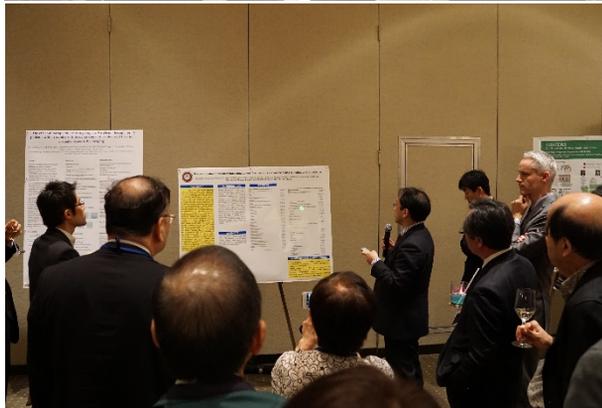
Web site; <http://curesarcoma.jp>

"CureSarcoma" was founded in June 2014. It is a nonprofit organization that supports patients and their families of soft tissue sarcomas (STS) in adults. The research of STS in adults falls behind other cancer research and it does not have any established treatments today.

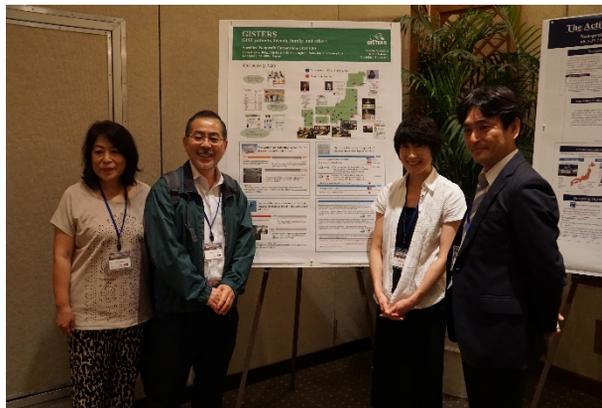
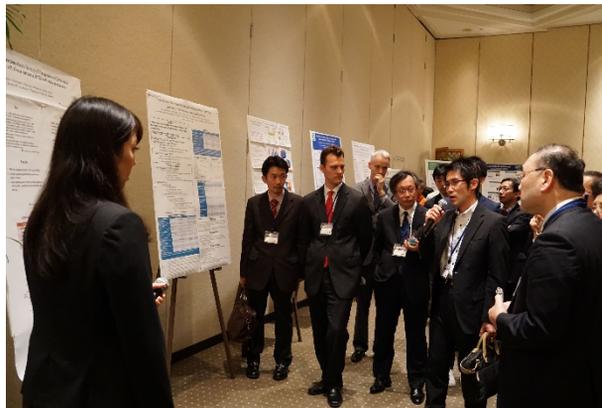
It is said that there are about 5 to 8 thousand people diagnosed as sarcoma in Japan. STS in adults in the thoracic and abdominal regions account for the majority, other than children's sarcoma and bone sarcoma. Chemotherapy and radiotherapy do not cure STS in adults. Even after the surgeries, sarcomas tend to relapse repeatedly and spreads, even in the lungs, liver and peritoneum. Because it has very unfavorable prognosis, patients are often lost, frightened, and disappointed. They feel very isolated because there are no other sarcoma patients around them. Furthermore, because sarcomas tend to relapse repeatedly, any treatments require time and money. High medical bills make patients and their families more anxious about their future.

Our main objective is to support patients by providing correct information they seek and help them establishing mutual communication with doctors and other patients. We are also very active fundraising for research and education for families and doctors. Most of our members lost their loved ones. Therefore, we sincerely hope that we can decrease some anxieties and hopelessness of patients to improve their overall quality of life.

## Photo galleries (7)



## Photo galleries (8)



## Photo galleries (9)



*Friday, December 5, 2014*

**9:00-12:00 (Hau Terrace)**

# **Frontiers in the Medical Oncology in Sarcoma –Past, Present and Future**

Moderators

Satoshi Teraoka

(International University of Health and Welfare, Japan)

Yukihiro Koike

(Kantou Central Hospital, Japan)

*The Japan-United States International Workshop  
on The Sarcoma Research and Therapy  
Halekulani, Honolulu, U.S.A.*



Robert G. Maki, M.D., Ph.D., FACP

Professor,  
Department of Pediatrics,  
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Medicine, Medical Oncology,  
Mount Sinai Hospital  
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## State of the Art Lecture

### Drug therapy for sarcoma – past, present and future

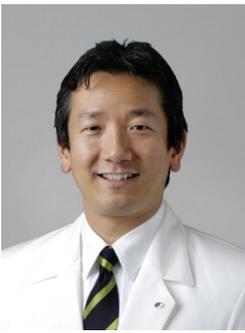
Robert Maki, Mt Sinai Medical Center, New York, NY, USA

**Background and Aims:** The status of sarcoma therapy is in constant flux, owing to the diverse nature of these cancers biologically. However, some general principles regarding systemic therapy still apply.

**Methods:** Presented is one viewpoint regarding systemic therapy for sarcomas, including GIST and other sarcomas in which small molecule oral kinase inhibitors (SMOKIs) are much less effective.

**Results:** Systemic therapy for GIST involves imatinib in the adjuvant setting for three years for higher risk tumors (SSG XVIII data from Joensuu et al). The three approved lines of therapy for metastatic disease in many countries include imatinib, sunitinib and regorafenib. For other primary sarcomas, only in the pediatric subtypes is adjuvant chemotherapy proved useful. For more common sarcomas in adulthood, such as undifferentiated pleomorphic sarcoma (UPS, formerly malignant fibrous histiocytoma, MFH) and leiomyosarcoma the benefit of adjuvant chemotherapy is much less, and requires discussion on a person by person basis. There are few data examining sarcomas of intraabdominal or intrathoracic sites, making recommendations on what are often diverse and high risk tumors very difficult. In the main, ifosfamide appears to be an important factor in adjuvant therapy based on a 2008 meta-analysis by Pervaiz; since dedifferentiated liposarcomas nearly always recur local-regionally and since leiomyosarcomas are not terribly sensitive to ifosfamide, it is not clear (also based on phase II data of adjuvant chemotherapy in uterine sarcomas) that chemotherapy is beneficial for intra-abdominal or retroperitoneal sarcomas. It is clearer that chemotherapy can delay a recurrence, however. Chemotherapy in the adjuvant setting is omitted for chemotherapy-insensitive subtypes, e.g. EHE, SFT, clear cell sarcoma and ASPS. For metastatic disease it is increasingly clear that chemotherapy must be administered with histology in mind. Endometrial stromal sarcoma responds to anti-estrogens, but there is very little activity in uterine leiomyosarcomas, despite their often having presence of ER. Doxorubicin, ifosfamide, gemcitabine-docetaxel, gemcitabine-dacarbazine are all standard chemotherapy agents or combinations with activity. Pazopanib is now approved in many countries for treatment of metastatic sarcoma refractory to prior therapy, but the exact reason it is active remains elusive; no single histology stands out as particularly responsive based on retrospective analysis of the PALETTE study, but relatively impressive responses have been seen in synovial sarcoma, leiomyosarcoma, and other diagnoses.

**Discussion and summary:** A greater focus on sarcoma subtype specific trials, or at least recognition of different subtypes in a single trial, is mandatory for successful trials in sarcoma in the future. Both GIST and studies by pediatrics groups in rhabdomyosarcoma, Ewing sarcoma, and osteogenic sarcoma point out the benefits of examining sarcomas on a histology-specific basis.



**Yu Oyama, M.D.**

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## **Chemotherapy and molecular-targeted therapy for sarcoma**

Yu Oyama, Oncology Center, Department of medical Oncology, Kameda General Hospital, Kameda Medical Center, Chiba, Japan

There are few established standard therapies in bone and soft-tissue sarcomas. Some of the standard chemotherapies also have many rooms for the improvement. In metastatic sarcomas, cytotoxic drugs have traditionally been used, but disease eventually progresses or there may be unacceptable toxicities after the several cycles even if the tumor is responding. The new drugs called molecularly-targeted therapies have been used in various malignancies with certain successes. VEGF inhibitors and mTOR inhibitors and CDK inhibitors have shown some promising activities in pre-and clinical trials in some sarcomas. Immune checkpoint inhibitors will be tested as well either alone or in combinations. More trials will eventually determine the true value of those new therapies in the future.



Hiroyuki Narahara, M.D., Ph.D.

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## **Pazopanib, an anti-angiogenesis therapy for sarcoma**

Hiroyuki Narahara,

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**Background and Aims:** We conducted a retrospective analysis on pazopanib for soft tissue sarcoma (STS) in order to examine the relationships of PFS with or without denosumab, also from the viewpoint of the first-line setting for metastatic diseases.

**Methods:** In this study, the patients with metastatic STS treated with pazopanib from November 2012 till July 2014, consecutively, were retrospectively analyzed. Among first 4 months, the starting dose was fixed at 800mg, but later changed to 400mg because of severe adverse events.

**Results:** Sixty eight patients (34 leiomyosarcomas, 6 liposarcomas, 28 other subtypes) were identified. Median age was 56 years old (range 17-81), 57 females and 11 males, 38 patients were treated in the first-line setting and 30 patients were in the second or later-line setting, and 21 patients with multiple bone metastases were all treated with denosumab, that is anti-RANKL antibody. All the patients included were evaluable by RECIST 1.1, and 37 patients were evaluated as PR/SD and 31 patients showed PD/NE. Median OS reached 16.9 months (95%CI: 9.7-ND) and median PFS was 2.6 months (95%CI: 2.2-3.7). From the viewpoint of PFS with response, PFS in PR and that in SD were similar. PFS showed no differences between 800mg vs 400mg, leiomyosarcoma vs liposarcoma vs others, PS 0/1 vs 2/3 and 1<sup>st</sup> line vs later line. But PFS in PR/SD was longer (4.9 months, 95%CI: 2.8-7.1) than that in PD/NE (1.7 months, 95%CI: 1.1-2.3,  $p<0.0001$ ). Finally, PFS with denosumab was not inferior to that without denosumab.

**Conclusions:** Pazopanib including first-line setting for metastatic STS is effective and comparable with EORTC trials. The combination chemotherapy of pazopanib with denosumab is promising and further investigations are warranted.



**Robin L. Jones, M.D., MRCP**

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## Recent advances and clinical trials of drug therapy in sarcoma

Robin L Jones, Associate Professor, Department of Medical Oncology, University of Washington/ Fred Hutchinson Cancer Research Center Seattle, U.S.A.

For many years doxorubicin with or without ifosfamide has been the standard systemic therapy for patients with inoperable or metastatic soft tissue sarcoma. Gemcitabine and docetaxel has emerged as an effective second line schedule, particularly for patients with leiomyosarcoma and pleomorphic sarcoma. Pazopanib has been approved for soft tissue sarcoma patients with disease that is refractory to anthracycline, based on the results of a randomized placebo controlled Phase III trial. In the European Union trabectedin has been approved as a salvage therapy in metastatic soft tissue sarcoma. In the United States a Phase III trial randomized patients with leiomyosarcoma and liposarcoma to receive trabectedin or dacarbazine with overall survival as the primary end point. Another Phase III trial in leiomyosarcoma and liposarcoma randomized patients to receive the micro tubule inhibitor, eribulin, or dacarbazine with progression-free survival as the primary end point. The results of these two trials are eagerly awaited. To enter these trials patients had to have received two prior lines of systemic therapy, or for the trabectedin trial anthracycline plus ifosfamide. In the first line setting, a large multicenter trial has randomized soft tissue sarcoma patients to receive doxorubicin with or without the hypoxia activated alkylating agent, TH-302. The primary end-point for this trial is overall survival. Within this trial patients can continue with TH-302 following 6 cycles of doxorubicin. Furthermore, a randomized Phase II trial evaluated the platelet derived growth factor receptor A (PDGFRA) inhibitor, olaratumab, in anthracycline naïve soft tissue sarcoma. Aldoxorubicin consists of doxorubicin attached to an acid sensitive linker that binds covalently to serum albumin. In a Phase Ib/II trial in the first line setting, randomizing patients to receive doxorubicin or aldoxorubicin, this novel agent showed promising activity. This has resulted in a large multicenter Phase III trial. Another Phase II trial randomized patients with soft tissue sarcoma to receive gemcitabine/ docetaxel with or without a monoclonal antibody to tumor endothelial marker-1 (TEM-1), with progression-free survival as the primary endpoint. In addition exploratory studies have shown the potential promise of immunotherapy in a number of sarcoma subtypes, including synovial and myxoid/round cell liposarcoma. Ongoing trials are also evaluating the role of CDK4 and MDM2 inhibitors in well- and dedifferentiated liposarcoma.

**Conclusions;** Much remains to be learned about these rare and heterogeneous malignancies. However, significant advances have been made, and the results of the trials discussed will hopefully lead to improved outcomes for patients with soft tissue sarcoma.

# Photo galleries (10)



## Photo galleries (11)



*Friday, December 5, 2014*

**12:00-12:15 (Hau Terrace)**

## **Closing Remarks**

Robert Maki, M.D., Ph.D. FRCP  
(Mount Sinai Hospital, New York, U.S.A.)

*The Japan-United States International Workshop  
on The Sarcoma Research and Therapy  
Halekulani, Honolulu, U.S.A.*



Robert G. Maki, M.D., Ph.D., FACP

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## Closing Remarks

Robert Maki, Mt Sinai Medical Center, New York, NY, USA

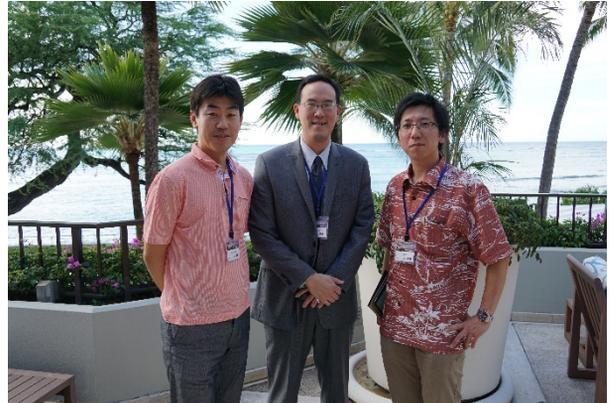
The cost of industrial clinical trials of chemotherapy drugs is now said to exceed US\$100 000 per patient. The rare nature of sarcomas makes them unattractive to industry to study given the even greater expense per patient of smaller sized clinical trials. Nonetheless there are a number of very interesting agents to be examined in sarcoma (as well as other cancers).

The author has discussed with many experts including clinicians and statisticians about how to better study as many sarcoma patients as possible.

While awaiting availability of some of the novel agents becoming available, simply structured clinical trials, even examining standard agents, allow more information to be gathered about specific agents in specific sarcoma subtypes. Even these data are useful to better understand how to sequence chemotherapy agents. Radiological data can be combined across institutions if staging imaging can be agreed upon between centers, to avoid lead time bias.

The use of small and efficient clinical trials minimizes the cost of clinical studies and allows gathering key data that will help in decision-making regarding our patients. Combining data from many centers allows progress to be made more efficiently, even in rare cancers. While waiting for novel agents to become available, we should make efforts to study every patient possible.

## Photo galleries (12)



# Patient Advocating Sarcoma Seminar

Shirakawa-go 2007



Kyoto 2011



Osaka 2012



Honolulu 2014

