

## Department of Surgery

### Division of Chest Surgery, Breast and Endocrinology Surgery

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#### Chest Surgery

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### General Summary

The Divisions of Chest Surgery and of Breast and Endocrinology Surgery were established in June 2005. Since then, all staff members have been active in surgical practice, research, and education. Many studies are ongoing.

### Research Activities

#### *Chest Surgery*

Thoracoscopic surgery is the focus of our clinical activity. This minimally invasive surgery produces fewer postoperative complications and sequelae and is especially beneficial for elderly, high-risk patients. Thoracoscopic surgery requires advanced skills, and we have independently developed total thoracoscopic surgery, which uses only a thoracoscope and video monitors to provide intraoperative views. Our method of thoracoscopic surgery can be used to treat many chest conditions, such as juvenile pneumothorax, peripheral lung nodules, mediastinal tumors, and lung cancer.

Thoracoscopic surgery is also indicated for higher-risk patients with such complications as advanced pulmonary emphysema, impaired pulmonary function, and extremely high age who are not candidates for conventional open surgery.

Operative procedures, including wedge resection, segmentectomy, lobectomy, and pneumonectomy of the lung, are all safely performed, in addition to resection of mediastinal tumors or the thymus. Surgery for lung cancer requires much more advanced skills and oncological considerations, which have also been independently developed. Of the mediastinal procedures, thymectomy is usually performed via thoracoscopy rather than via a conventional median sternotomy. In our department the percentage of the chest operations performed via thoracoscopy is more than 90%, which we assume to be the highest rate in the world.

The minimal invasiveness of thoracoscopic surgery is being investigated with prospective clinical studies. These studies include a comparative study of open surgery and video-assisted surgery for lung cancer and evaluations of video-assisted surgery for bullous lung diseases in elderly patients with impaired lung function, of video-assisted surgery for thymic tumors, and of video-assisted thymectomy for myasthenia gravis.

Our clinical studies are also evaluating new devices and methods, such as narrow-band imaging for the thoroscopic diagnosis of benign and malignant lung diseases, and LaparoSonic coagulating shears (Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA) for small thoracotomy. Three-dimensional diagnosis with computed tomography is used to make thoroscopic surgery safer. The diagnosis and treatment of ground glass opacity of the lung, which is considered to indicate early adenocarcinoma, are being evaluated.

Many basic research studies are also underway. In the morphological expression-related advancement of the molecular genetic analysis of lung cancer, we are investigating whether carcinogenesis of the lung as reflected by CA19-9 activity is an important marker of de novo carcinogenesis. The biological and genetic characteristics of peripheral adenocarcinoma of the lung are being investigated to establish the most appropriate surgical procedures. Correlation with the detection of blood CTC (Circulating Tumor Cells) and the prognosis of the patient with lung cancer is examined.

The oncogene of the lung cancer is analyzed with the next generation sequencer.

A system for viewing videos on the Internet is now being developed which will help improve surgical training and research.

### *Breast*

#### 1. Clinical study

##### 1) The evaluation of sentinel node biopsy after neoadjuvant chemotherapy

The minimally invasive technique of sentinel lymph node biopsy produces less morbidity and allows accurate pathologic staging of the axilla. Experience with sentinel node biopsy after neoadjuvant chemotherapy is limited. The purpose of our clinical study is to evaluate the accuracy and safety of this procedure in breast cancer patients after neoadjuvant chemotherapy.

##### 2) Evaluation of the effectiveness of exercise for psychiatric illness in patients after surgery for breast cancer

Many women experience the psychiatric illness such as emotional distress, depression and anxiety after a diagnosis of breast cancer. We have prospectively investigated the effects of exercise on psychological health.

##### 3) Cryotherapy for small breast cancer

Cryoablation using extremely cold temperatures to destroy tumor tissues has been increasingly recognized as a highly efficient cancer therapy. Therefore, cryotherapy has been used in the clinic to treat several types of tumors, including breast, kidney, liver, esophagus, skin, prostate, lung and bone. Moreover, the efficiency of cryotherapy, combined with its limited side-effects, has been confirmed through pilot studies with early-stage breast cancer patients.

##### 4) Therapeutic strategy for oligometastatic breast cancer

We have analyzed the patients with metastatic breast cancer for thirty years. The analyses indicate that oligometastatic breast cancer is a distinct subgroup with long-term prognosis superior to metastatic breast cancer. We try further prospective studies to better characterize oligometastatic breast cancer to improve prognosis in metastatic breast cancer.

#### 2. Basic research

##### 1) Development of breast cancer

We have investigated biological factors involved in the progression of carcinoma in situ to invasive breast cancer using the immunohistochemical techniques.

2) Clinically useful biomarkers for triple negative breast cancer

Triple negative breast cancer is heterogeneous disease. We have investigated prognostic and predictive biomarkers for triple negative breast cancer.

3) CTC and DTC

We had investigated clinical values of the presence of circulating tumor cells in the peripheral blood and disseminated tumor cells in the bone marrow (DTC-BM) of patients with early breast cancer. Detection of DTC-BMs was useful for observing adjuvant therapy effects and for predicting relatively late-phase metastasis. The cluster status of CTCs suggested early relapsing.

4) Cancer stem-cell

We evaluated the association of presence of cancer stem cell between primary breast tumor and metastatic site and the correlation with prognosis.

5) Dual Specificity Tyrosine Phosphorylation Regulated Kinase 2 (DYRK2)

We have evaluated the association between DYRK2 and stem cell or mTOR signal. The ectopic expression of DYRK2 promoted phosphorylation of Thr631 for the ubiquitination and degradation of mTOR. DYRK2 expression levels might thus predict clinical responses to everolimus. Furthermore, DYRK2 was a novel negative regulator for formation of breast cancer stem cells. Downregulation of DYRK2 promoted cancer stem-like traits in vitro, tumorigenesis in vivo and the proportion of the cancer stem cell population in human breast cancer tissues. We found that Kruppel-like factor 4 (KLF4) serves as a key mediator of DYRK2's control over the cancer stem phenotype. Reduced DYRK2 expression increased KLF4 expression, which induced cancer stem-like properties. We identified androgen receptor (AR) as a transcription factor binding to the KLF4 promoter region; this process was dependent on DYRK2 kinase activity. Our findings delineated a mechanism of cancer stem cell regulation by the DYRK2-AR-KLF4 axis in breast cancer. Targeting of this pathway might be a promising strategy against breast cancer stem cells.

*Endocrine*

*Clinical research*

Lenvatinib is one of tyrosine kinase inhibitor, which blocks VEGF Receptor1-3kinase. Lenvatinib had developed in Japan, and prolonged the progression free survival (PFF) to, in phase III trial.

We are planning and going a multi-center clinical trial for thyroid carcinomas, including papillary carcinoma, medullary carcinoma, and undifferentiated carcinoma to confirm the antitumor effects of Lenvatinib in thyroid carcinoma treated major facilities of Japan from 2016.

Our department is joining to this trial from 2016.

*Basic research*

The detection of antigens of thyroid carcinoma in sera.

A monoclonal antibody, designated JT-95, was made against a thyroid papillary carci-

noma obtained by our Department of Breast and Endocrine Surgery. We are attempting to measure the antigen recognized by JT-95 in the serum of patients with papillary carcinoma, in collaboration with the Molecular Cell Biology Division of Jikei University. The quantity of antigen of JT-95 is higher in patients with papillary carcinoma, especially those with metastasis to lung or bone, than in patients with breast carcinoma. We are now trying to make chromatography of JT-95 to detect thyroid carcinoma antigen more easily.

## Publications

**Odaka M, Shibasaki T, Kato D, Mori S, Asano H, Yamashita M, Morikawa T.** Comparison of oncological results for early- and advanced-stage thymomas: thoracoscopic thymectomy versus open thymectomy. *Surg Endosc.* 2017; **31**: 734-42.

**Odaka M, Tsukamoto Y, Shibasaki T, Katou D, Mori S, Asano H, Yamashita M, Morikawa T.** Thoracoscopic thymectomy is a feasible and less invasive alternative for the surgical treatment of large thymomas. *Interact Cardiovasc Thorac Surg.* 2017; **25**: 103-8. Epub 2017 Mar 23.

**Mori S, Motoi N<sup>1</sup>, Ninomiya H<sup>1</sup>, Matsuura Y<sup>1</sup>, Nakao M<sup>1</sup>, Mun M<sup>1</sup>, Okumura S<sup>1</sup>, Nishio M<sup>1</sup>, Morikawa T, Ishikawa Y<sup>1</sup> (The Cancer Institute Hospital).** High expression of programmed cell death 1 ligand 1 in lung adenocarcinoma is a poor prognostic factor particularly in smokers and wild-type epidermal growth-factor receptor cases. *Pathol Int.* 2017; **67**: 37-44.

**Takeyama H, Shimada T, Kinoshita S, Uchida K.** Usefulness of CTC and DTC-BM Detection for Adjuvant Therapy Effects and Prognosis Prediction in Early Breast Carcinoma: Results of 8-11 Years of Follow-up Evaluation. *Ann Surg Oncol.* 2017; **24**: 1227-33. Epub 2016 Dec 1.

**Kinoshita S, Fukushima N, Miyake R, Ishigaki T, Hirano A, Mimoto R, Uchida K, Takeyama H, Morikawa T.** Clinicopathological assessment of patients with locally advanced breast cancer with 10 or more lymph node metastases. *Breast Can Curr Res.* 2016; **1**: 107.

**Kinoshita S, Nojima K, Miyake R, Shimada N, Hirano A, Uchida K, Takeyama H, Morikawa T.** Clinical assessment of skin incisions used for skin-sparing mastectomy. *Intern Med Rev.* 2016; **2**: 197.

**Kawase K, Carpelan-Holmström M (Helsinki University Central Hospital), Kwong A (The University of Hong Kong), Sanfey H (SIU School of Medicine).** Factors that can promote or impede the advancement of women as leaders in surgery: results from an international survey. *World J Surg.* 2016; **40**: 258-6.

**Yorozuya K<sup>1</sup>, Kawase K, Akashi-Tanaka S<sup>2</sup>, Kanbayashi C<sup>3</sup>, Nomura S<sup>1</sup>, Tomizawa Y<sup>6</sup> (Kawasaki Municipal Hospital, <sup>2</sup>Showa University Hospital, <sup>3</sup>Niigata Cancer Center Hospital, <sup>4</sup>Univ Tokyo, <sup>5</sup>Tokyo Women's Medical Univ).** Mentorship as Experienced by Women Surgeons in Japan. *World J Surg.* 2016; **40**: 38-44.

## Reviews and Books

**Odaka M, Shibasaki T, Kato D, Mori S, Asano H, Yamashita M, Morikawa T.** Surgical and oncological outcomes of thoracoscopic thymectomy for thymoma. *J Vis Surg.* 2017; **3**: 54.

**Kinoshita S, Nojima K, takeyama H, Uchida K.** Four types of skin incisions for skin-sparing mastectomy with immediate breast reconstruction. In: Shiffman MA, editor. *Breast Reconstruction: art, science, and new clinical techniques.* New York: Springer; 2016. p. 547-54.